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(54) **SUBSTITUTED PYRIDINE AND PYRIMIDINE DERIVATIVES AND THEIR USE IN TREATING VIRAL INFECTIONS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,470,834 B2	6/2013	Kwong et al.
8,541,434 B2	9/2013	Kwong et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO	0248148 A2	6/2002
WO	2007031977 A2	3/2007
WO	WO 2010022121 A1 *	2/2010

OTHER PUBLICATIONS

Ago, et al, Crystal Structure of the RNA-Dependent RNA Polymerase of Hepatitus C Virus, Structure, 1999, pp. 1416-1426, vol. 7, WO.

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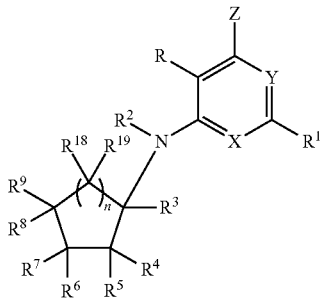
(57) **ABSTRACT**

The present invention provides compounds of Formula (I): and tautomers, isomers, and esters of said compounds, and pharmaceutically acceptable salts, solvates, and prodrugs of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and n is selected independently and as defined herein. Compositions comprising such compounds are also provided. The compounds of the invention are effective as inhibitors of HCV, and are useful, alone and together with other therapeutic agents, in treating or preventing diseases or disorders such as viral infections and virus-related disorders.

(I)



7 Claims, No Drawings

(51) **Int. Cl.**

A01N 37/18	(2006.01)
A61K 38/00	(2006.01)
A61P 1/16	(2006.01)
A61K 51/00	(2006.01)
A61M 36/14	(2006.01)
A61K 31/506	(2006.01)
A61K 45/06	(2006.01)
C07D 403/04	(2006.01)
C07D 413/04	(2006.01)
C07D 417/04	(2006.01)
C07D 491/048	(2006.01)
C07D 513/04	(2006.01)
C07D 417/14	(2006.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,697,694	B2	4/2014	Arasappan et al.
8,715,638	B2	5/2014	Kwong et al.
2009/0247523	A1	10/2009	Raboisson et al.
2010/0003213	A1	1/2010	Devos et al.

* cited by examiner

SUBSTITUTED PYRIDINE AND PYRIMIDINE DERIVATIVES AND THEIR USE IN TREATING VIRAL INFECTIONS

FIELD OF THE INVENTION

The present invention relates to certain substituted pyridine and pyrimidine derivatives, to compositions comprising them, and to methods for their use as inhibitors of HCV and in treating or preventing viral infections or virus-related disorders.

BACKGROUND OF THE INVENTION

HCV is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH). NANBH is distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis delta virus (HDV), as well as from other forms of liver disease such as alcoholism and primary biliary cirrhosis.

Hepatitis C virus is a member of the hepacivirus genus in the family Flaviviridae. It is the major causative agent of non-A, non-B viral hepatitis and is the major cause of transfusion-associated hepatitis and accounts for a significant proportion of hepatitis cases worldwide. Although acute HCV infection is often asymptomatic, nearly 80% of cases resolve to chronic hepatitis. About 60% of patients develop liver disease with various clinical outcomes ranging from an asymptomatic carrier state to chronic active hepatitis and liver cirrhosis (occurring in about 20% of patients), which is strongly associated with the development of hepatocellular carcinoma (occurring in about 1-5% of patients). The World Health Organization estimates that 170 million people are chronically infected with HCV, with an estimated 4 million living in the United States.

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection remains poor as HCV infection is more difficult to treat than other forms of hepatitis. Current data indicate a four-year survival rate of below 50% for patients suffering from cirrhosis and a five-year survival rate of below 30% for patients diagnosed with localized resectable hepatocellular carcinoma. Patients diagnosed with localized unresectable hepatocellular carcinoma fare even worse, having a five-year survival rate of less than 1%.

Replication of HCV is thought to occur in membrane-associated replication complexes. Within these, the genomic plus-strand RNA is transcribed into minus-strand RNA, which in turn can be used as a template for synthesis of progeny genomic plus-strands. At least two viral enzymes appear to be involved in this reaction: the NS3 helicase/NTPase, and the NS5B RNA-dependent RNA polymerase. While the role of NS3 in RNA replication is less clear, NS5B is the key enzyme responsible for synthesis of progeny RNA strands. Using recombinant baculoviruses to express NS5B in insect cells and a synthetic nonviral RNA as a substrate, two enzymatic activities have been identified as being associated with it: a primer-dependent RdRp and a terminal transferase (TNTase) activity. It was subsequently confirmed and further characterized through the use of the HCV RNA genome as a substrate. Other studies have shown that NS5B with a C-terminal 21 amino-acid truncation expressed in *Escherichia coli* is also active for in vitro RNA synthesis. On certain RNA templates, NS5B has been shown to catalyze RNA synthesis via a de novo initiation mechanism, which has been postulated to be the mode of viral replication in vivo. Templates with single-stranded 3' termini, especially those containing a 3'-terminal cytidylate moiety, have been found to direct de novo synthesis efficiently. There has also been evidence for NS5B to utilize di- or tri-nucleotides as short primers to initiate replication.

Particular therapies for HCV infection include α-interferon monotherapy and combination therapy comprising α-interferon and ribavirin. These therapies have been shown to be effective in some patients with chronic HCV infection. The use of antisense oligonucleotides for treatment of HCV infection has also been proposed as has the use of free bile acids, such as ursodeoxycholic acid and chenodeoxycholic acid, and conjugated bile acids, such as tauroursodeoxycholic acid. Phosphonoformic acid esters have also been proposed as potentially for the treatment of various viral infections including HCV. Vaccine development, however, has been hampered by the high degree of viral strain heterogeneity and immune evasion and the lack of protection against reinfection, even with the same inoculum.

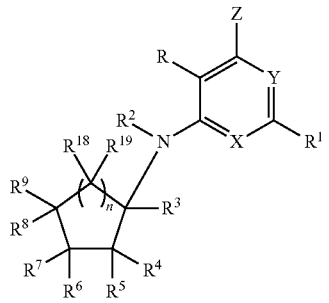
NS5B, the RNA-dependent RNA polymerase, is an important and attractive target for small-molecule inhibitors. Studies with pestiviruses have shown that the small molecule compound VP32947 (3-[((2-dipropylamino)ethyl) thio]-5H-1,2,4-triazino[5,6-b]indole) is a potent inhibitor of pestivirus replication and most likely inhibits the NS5B enzyme since resistant strains are mutated in this gene. Inhibition of RdRp activity by (−)β-L-2',3'-dideoxy-3'-thiacytidine 5'-triphosphate (3TC; lamivudine triphosphate) and phosphonoacetic acid also has been observed.

SUMMARY OF THE INVENTION

The present invention provides certain substituted pyridine and pyrimidine derivatives (collectively referred to herein as "compounds of the invention"), compositions comprising such compounds, and methods for their use as HCV inhibitors and for treating viral infections and disorders related thereto.

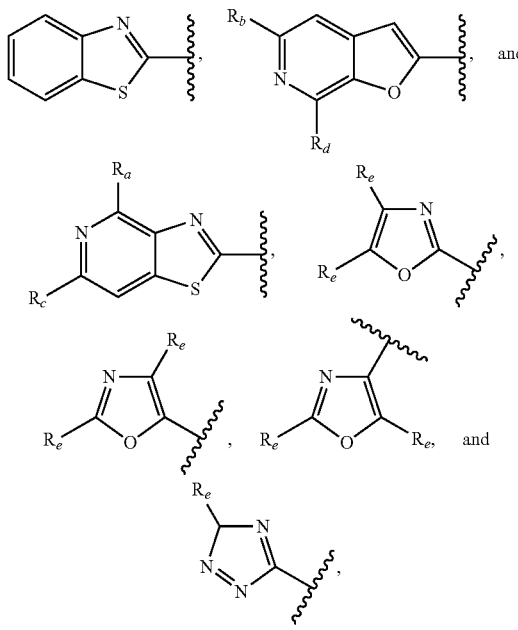
In one embodiment, the compounds of the invention have a general structure shown in Formula (I):

(I)



and include tautomers, isomers, and esters of said compounds, and pharmaceutically acceptable salts, solvates, and prodrugs of said compounds, tautomers, isomers, and esters, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and n are selected independently and wherein:

R is selected from the group consisting of:



and N-oxides thereof,

wherein:

R_a (when present) is selected from the group consisting of H, —OH, Me, Et, —OMe, —OEt, —CH_2—CH_2—CN, —CH_2—CH_2—C(O)OH, —CH_2—CH_2—C(O)OMe, —CH_2—CH_2—C(O)OEt, —CH_2—$C(CH_3)_3$, n-propyl, i-propyl, i-butyl, cyclopropyl, cyclobutyl, —NH_2, —CH_2—NH_2;

R_b (when present) is selected from the group consisting of H, Me, Et, n-propyl, —OMe, and —OEt;

R_c (when present) is selected from the group consisting of H, Me, Et, and cyclopropyl;

R_d (when present) is selected from the group consisting of H, Me, and Et; and

each R_e (when present) is independently selected from the group consisting of phenyl and benzyl;

X and Y are each independently selected from N and CH, with the proviso that at least one of X or Y is N;

Z=H, halo, —OH, —SH, —CN, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, heterohaloalkyl, —S-alkyl, —O-alkyl, —O-aryl, —O-heteroaryl, cycloalkyl, aryl, heteroaryl, —NH_2, —NHR^{12}, and —$NR^{12}R^{13}$;

R^1 is selected from H, halo, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, heteroaryl, —OH, —O-alkyl, —O-aryl, —O-heteroalkyl, —O-heteroaryl, —SH, —S-alkyl, —S-aryl, —S-heteroalkyl, —S-heteroaryl, —NH_2, —NHR^{14}, —$NR^{14}R^{15}$, —NO_2, —S(O)NHR^{10}, —S(O)$NR^{10}R^{11}$, —S(O)R^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$;

R^2 (when R^2 is not joined with R^9) is selected from H and alkyl;

n=0, 1, or 2;

R^3 is selected from H, -alkyl, -alkenyl, alkynyl, aryl, heteroaryl, and cycloalkyl,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, and said cycloalkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^4 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —C(O)OR^{10}, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —S(O)NHR^{10}, —S(O)$NR^{10}R^{11}$, —S(O)R^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^5 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —C(O)OR^{10}, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —S(O)NHR^{10}, —S(O)$NR^{10}R^{11}$, —S(O)R^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, R^4 and R^5 are taken together with the carbon atom to which they are shown attached to form a 3- to 7-membered, saturated or partially unsaturated, spirocycloalkyl ring containing from 0 to 3 spiro ring heteroatoms selected from O, N, and S;

R^6 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —C(O)OR^{10}, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —S(O)NHR^{10}, —S(O)$NR^{10}R^{11}$, —S(O)R^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-ha-

loalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, R^5 and R^6 are taken together to form a double bond;

R^7 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)NHR^{10}$, —$S(O)NR^{10}R^{11}$, —$S(O)R^{10}$, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, R^6 and R^7 are taken together with the carbon atom to which they are shown attached to form a 3- to 7-membered, saturated or partially unsaturated, spirocycloalkyl ring containing from 0 to 3 spiro ring heteroatoms selected from O, N, and S;

R^8 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)NHR^{10}$, —$S(O)NR^{10}R^{11}$, —$S(O)R^{10}$, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-cycloalkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —O(C)O—N(R^{10})R^{11}, —O(C)O—NHR^{11}, —O(C)O—NH_2, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, —$N(R^{10})S(O)_2R^{10}$, —$NHS(O)_2R^{10}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^9 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)NHR^{10}$, —$S(O)NR^{10}R^{11}$, —$S(O)R^{10}$, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-cycloalkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —O(C)O—N(R^{10})R^{11}, —O(C)O—NHR^{11}, —O(C)O—NH_2, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, —$N(R^{10})S(O)_2R^{10}$, —$NHS(O)_2R^{10}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, R^8 and R^9 are taken together with the carbon atom to which they are shown attached to form a 3- to 7-membered, saturated or partially unsaturated, spirocycloalkyl ring containing from 0 to 3 spiro ring heteroatoms selected from O, N, and S;

each R^{18} (when present) is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)NHR^{10}$, —$S(O)NR^{10}R^{11}$, —$S(O)R^{10}$, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

each R^{19} (when present) is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)NHR^{10}$, —$S(O)NR^{10}R^{11}$, —$S(O)R^{10}$, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

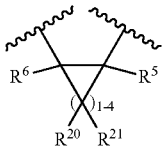
wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, n is 1 and R^{18} and R^{19} are taken together with the carbon atom to which they are attached to form

a 3- to 7-membered, saturated or partially unsaturated, spirocycloalkyl ring containing from 0 to 3 spiro ring heteroatoms selected from O, N, and S;

or, alternatively, R^4 and R^7, together with the carbon atoms to which they are shown attached, form a moiety (1C):

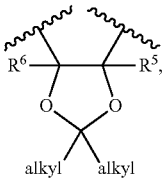
(1C)



wherein R^{20} and R^{21} are each independently selected from H, alkyl, and heteroalkyl and wherein R^5 and R^6 are defined above, with the proviso that when R^4 and R^7 form a moiety (1C), then R^5 and R^6 are not taken together to form a double bond;

or, alternatively, R^4 and R^7, together with the carbon atoms to which they are shown attached, form a moiety (1D):

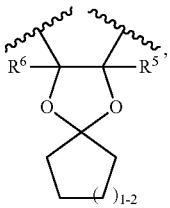
(1D)



wherein R^5 and R^6 are as defined above;

or, alternatively, R^4 and R^7, together with the carbon atoms to which they are shown attached, form a moiety (1E):

(IE)



wherein R^5 and R^6 are as defined above;

each R^{10} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)N(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

each R^{11} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)N(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{10} and R^{11} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- or 6-membered heterocycloalkyl;

each R^{12} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)N(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

each R^{13} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)N(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{12} and R^{13} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- to 6-membered heterocycloalkyl;

each R^{14} is independently selected from alkyl, alkoxy, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, alkylamino, alkylthio, heteroalkenyl, haloalkenyl, —$S(O)_2$-alkyl, -alkyl-OH, -alkyl-O-Acyl, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, cycloalkyl-alkyl-, heterocycloalkyl, heterocycloalkyl-alkyl-, heterocycloalkenyl, heterocycloalkenyl-alkyl-, aryl, aryl-alkyl-, heteroaryl, and heteroaryl-alkyl-,

wherein each said alkyl, each said alkoxy, each said alkenyl, each said haloalkyl, each said heteroalkyl, each said heterohaloalkyl, each said alkylamino, each said alkylthio, each said heteroalkenyl, each said haloalkenyl, each said —$S(O)_2$-alkyl, each said -alkyl-OH, each said -alkyl-O-Acyl, each said —C(O)Oalkyl, each said —C(O)alkyl, each said cycloalkyl, each said cycloalkyl-alkyl-, each said heterocycloalkyl, each said heterocycloalkyl-alkyl-, each said heterocycloalkenyl, each said heterocycloalkenyl-alkyl-, each said aryl, each said aryl-alkyl-, each said heteroaryl, and each said heteroaryl-alkyl-, is unsubstituted or optionally independently substituted with from one to five substituent, which can be the same or different, each substitutent being independently selected from —OH, halo, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)_2$alkyl, —$S(O)_2$aryl, alkyl, alkoxy, haloalkyl, heteroalkyl, haloalkoxy, heteroaryl, heterohaloalkyl, aryl, cycloalkyl, and heterocycloalkyl;

each R^{15} is independently selected from alkyl, alkoxy, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, alkylamino, alkylthio, heteroalkenyl, haloalkenyl, —$S(O)_2$-alkyl, -alkyl-OH, -alkyl-O-Acyl, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, cycloalkyl-alkyl-, heterocycloalkyl, heterocycloalkyl-alkyl-, heterocycloalkenyl, heterocycloalkenyl-alkyl-, aryl, aryl-alkyl-, heteroaryl, and heteroaryl-alkyl-,

wherein each said alkyl, each said alkoxy, each said alkenyl, each said haloalkyl, each said heteroalkyl, each said heterohaloalkyl, each said alkylamino, each said alkylthio, each said heteroalkenyl, each said haloalkenyl, each said —$S(O)_2$-alkyl, each said -alkyl-OH, each said -alkyl-O-Acyl, each said —C(O)Oalkyl, each said —C(O)alkyl, each said cycloalkyl, each said cycloalkyl-alkyl-, each said heterocycloalkyl, each said heterocycloalkyl-alkyl-, each said heterocycloalkenyl, each said heterocycloalkenyl-alkyl-, each said aryl, each said aryl-alkyl-, each said heteroaryl, and each said heteroaryl-alkyl-, is unsubstituted or optionally independently substituted with from one to five substituent, which can be the same or different, each substitutent being independently selected from —OH, halo, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —$C(O)OR^{10}$, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$S(O)_2$alkyl, —$S(O)_2$aryl, alkyl, alkoxy, haloalkyl, haloalkoxy, heteroaryl, heteroalkyl, heterohaloalkyl, aryl, cycloalkyl, and heterocycloalkyl;

or, alternatively, R^{14} and R^{15} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- to 6-membered heterocycloalkyl;

each R^{16} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —C(O)N(alkyl)$_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl; and

each R^{17} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —C(O)N(alkyl)$_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{16} and R^{17} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- or 6-membered heterocycloalkyl.

In another embodiment, the invention provides compositions, including pharmaceutical compositions, comprising one or more compounds of the invention (e.g., one compound of the invention), or a pharmaceutically acceptable salt, solvate, ester, or prodrug thereof, and a pharmaceutically acceptable carrier or diluent. In one embodiment, said compound or compounds of the invention are present in the composition in an amount effective for inhibiting HCV, and/or for treating or preventing a viral infection or a virus-related disorder in a patient in need thereof.

In another embodiment, the invention provides a pharmaceutical composition comprising one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, ester, or prodrug thereof, together with one or more additional therapeutic agents, optionally further comprising a pharmaceutically effective carrier or diluent. Non-limiting examples of such additional therapeutic agents include one or more of any of the following: HCV polymerase inhibitors, HCV protease inhibitors, HCV replicase inhibitors, nucleosides, Interferon, and/or ribavirin (or Levovirin or Viramidine). Non-limiting examples of interferon include PEG-interferon, PEG interferon alpha conjugate, alpha-interferon, and pegylated interferon. These and other examples are known to those of ordinary skill in the art.

In another embodiment, the present invention provides for the use of one or more compounds of the invention, or a pharmaceutically acceptable salt, solvate, ester, and/or prodrug thereof, alone or in combination with one or more additional therapeutic agents such as those described above, for inhibiting HCV and/or for treating or preventing a viral infection or a virus-related disorder in a patient in need thereof.

In another embodiment, the invention provides a method of inhibiting HCV in vivo, ex vivo, or in vitro, comprising exposing a population of cells comprising HCV to an effective amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester, or prodrug thereof, alone or in combination with one or more additional therapeutic agents such as those described above. In one such embodiment, the compound or compounds of the invention are used as the neat chemical. In another such embodiment, the compounds of the invention are used in the form of a pharmaceutically acceptable composition.

In another embodiment, the invention provides a method for treating or preventing a viral infection or a virus-related disorder in a patient, comprising administering to the patient an effective amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester, or prodrug thereof, alone or in combination with one or more additional therapeutic agents such as those described above. In one such embodiment, the compound or compounds of the invention are used as the neat chemical. In another such embodiment, the compounds of the invention are used in the form of a pharmaceutically acceptable composition.

The details of the invention are set forth in the accompanying detailed description below. Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are described herein. Other features, objects, and advantages of the invention will be apparent from the description and the claims. All patents and publications cited in this specification are incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the compounds of the invention have the structural Formula (I) as described above, and include pharmaceutically acceptable salts, esters, prodrugs, tautomers, and isomers of said compounds.

In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H.

In one embodiment, in Formula (I), n is 1; each of R^2, R^3, R^5, R^6, R^8, R^{18} and R^{19} is H; R^4 and R^7 are OH; and R^9 is alkyl, wherein said alkyl is unsubstituted or substituted with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-cycloalkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl.

In one embodiment, in Formula (I), n is 1; each of R^2, R^3, R^5, R^6, R^8, R^{18} and R^{19} is H; R^4 and R^7 are OH; and R^9 is alkyl, wherein said alkyl is unsubstituted or substituted with from one to five groups independently selected from —OH, halo, —CN, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, —Oalkyl, —Ocycloalkyl, —O-alkyl-cycloalkyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, and —$S(O)_2NR^{10}R^{11}$.

In one embodiment, in Formula (I), n is 1; each R^2, R^3, R^5, R^6, R^8, R^{18} and R^{19} is H; R^4 and R^7 are OH; and R^9 is methyl, wherein said methyl is unsubstituted or substituted with from one to three groups independently selected from —OH, halo, alkyl, —CN, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, —Oalkyl, -Ocycloalkyl, —O-alkyl-cycloalkyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, and —$S(O)_2NR^{10}R^{11}$.

In some embodiments, R^9 is -alkyl-$NHS(O)_2R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, R^9 is selected from -alkyl-$N(CH_3)S(O)_2R^{10}$ and -alkyl-$N(CH_2CH_3)S(O)_2R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, R^9 is -alkyl-O(C)O—NHR^{10}, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, R^9 is selected from R^9-alkyl-O(C)O—$N(CH_3)R^{10}$ and —O(C)O—$N(CH_2CH_3)R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In one embodiment, in Formula (I), n is 1; each of R^2, R^3, R^5, R^6, R^8, R^{18} and R^{19} is H; R^4 and R^7 are OH; and R^9 is selected from —CH_2—O-alkyl, —CH_2—OH, —CH_3, H,

—CH_2—CH_3, —CH_2—$OC(O)CF_3$, —CH_2—NH_2, —CH_2—NHR^{16}, and —CH_2—$NR^{16}R^{17}$.

In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H and each of R^4 and R^7 is —OH.

In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H; each of R^4 and R^7 is —OH; and R^9 is —O-alkyl.

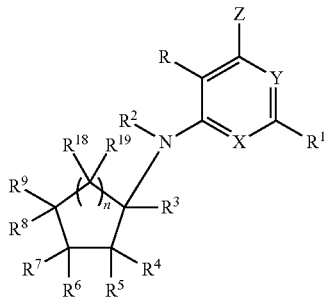
In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H; each of R^4 and R^7 is —OH; and R^9 is —O—CH_3.

In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H; each of R^4 and R^7 is —OH; R^9 is —O—CH_3, and n is 1.

In one embodiment, in Formula (I), each of R^3, R^5, R^6, and R^8 is H; each of R^4 and R^7 is —OH; R^9 is —O—CH_3, and n is 2.

In one embodiment, the compounds of the invention have the structural Formula (I.A):

(I.A)



and includes tautomers, isomers, and esters of such compounds, and pharmaceutically acceptable salts, solvates, and prodrugs of said compounds, tautomers, isomers, and esters, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and n are selected independently and wherein:

R, R^1, R^2, X, Y, Z, and n are as defined in Formula (I);

R^3 is selected from H, -alkyl, -alkenyl, alkynyl, aryl, heteroaryl, and cycloalkyl,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, and said cycloalkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^4 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^5 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl,

R^6 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^7 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

or, alternatively, R^6 and R^7 are taken together with the carbon atom to which they are shown attached to form a 3- to 7-membered, saturated or partially unsaturated, spirocycloalkyl ring containing from 0 to 3 spiro ring heteroatoms selected from O, N, and S;

R^8 is selected from is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted

with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, alkyl, —O-alkyl, —S-alkyl, —$S(O)_2$-alkyl, —$S(O)_2NH_2$, —$S(O)_2$NHalkyl, —$S(O)_2N(alkyl)_2$, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

R^9 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, alkyl, —O-alkyl, —S-alkyl, —$S(O)_2$-alkyl, —$S(O)_2NH_2$, —$S(O)_2$NHalkyl, —$S(O)_2N(alkyl)_2$, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

each R^{18} (when present) is independently selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

each R^{19} (when present) is independently selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NHalkyl, and —$N(alkyl)_2$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl, is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, —O-alkyl, —O-alkenyl, -haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl;

each R^{10} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

each R^{11} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, —C(O)NHalkyl, —$C(O)(alkyl)_2$, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{10} and R^{11} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- or 6-membered heterocycloalkyl;

each R^{12} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

each R^{13} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{12} and R^{13} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- to 6-membered heterocycloalkyl;

each R^{14} is independently selected from alkyl, alkoxy, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, alkylamino, heteroalkenyl, haloalkenyl, —$S(O)_2$-alkyl, -alkyl-OH, -alkyl-O-Acyl, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, cycloalkyl-alkyl-, heterocycloalkyl, heterocycloalkyl-alkyl-, heterocycloalkenyl, heterocycloalkenyl-alkyl-, aryl, aryl-alkyl-, heteroaryl, and heteroaryl-alkyl-,

wherein each said alkyl, each said alkoxy, each said alkenyl, each said haloalkyl, each said heteroalkyl, each said heterohaloalkyl, each said alkylamino, each said heteroalkenyl, each said haloalkenyl, each said —$S(O)_2$-alkyl, each said -alkyl-OH, each said -alkyl-O-Acyl, each said —C(O)Oalkyl, each said —C(O)alkyl, each said cycloalkyl, each said cycloalkyl-alkyl-, each said heterocycloalkyl, each said heterocycloalkyl-alkyl-, each said heterocycloalkenyl, each said heterocycloalkenyl-alkyl-, each said aryl, each said aryl-alkyl-, each said heteroaryl, and each said heteroaryl-alkyl-, is unsubstituted or optionally independently substituted with from one to three substituent, which can be the same or different, each substitutent being independently selected from halo, —OH, —NH_2, —NHalkyl, —$N(alkyl)_2$, alkyl, alkoxy, haloalkyl, haloalkoxy, heteroaryl, heteroalkyl, and heterohaloalkyl;

each R^{15} is independently selected from alkyl, alkoxy, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, alkylamino, heteroalkenyl, haloalkenyl, —$S(O)_2$-alkyl, -alkyl-OH, -alkyl-O-Acyl, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, cycloalkyl-alkyl-, heterocycloalkyl, heterocycloalkyl-alkyl-, heterocycloalkenyl, heterocycloalkenyl-alkyl-, aryl, aryl-alkyl-, heteroaryl, and heteroaryl-alkyl-,

wherein each said alkyl, each said alkoxy, each said alkenyl, each said haloalkyl, each said heteroalkyl, each said heterohaloalkyl, each said alkylamino, each said heteroalkenyl, each said haloalkenyl, each said —$S(O)_2$-alkyl, each said -alkyl-OH, each said -alkyl-O-Acyl, each said —C(O)Oalkyl, each said —C(O)

alkyl, each said cycloalkyl, each said cycloalkyl-alkyl-, each said heterocycloalkyl, each said heterocycloalkyl-alkyl-, each said heterocycloalkenyl, each said heterocycloalkenyl-alkyl-, each said aryl, each said aryl-alkyl-, each said heteroaryl, and each said heteroaryl-alkyl-, is unsubstituted or optionally independently substituted with from one to three substituent, which can be the same or different, each substitutent being independently selected from halo, —OH, —NH_2, —NHalkyl, —$N(alkyl)_2$, alkyl, alkoxy, haloalkyl, haloalkoxy, heteroaryl, heteroalkyl, and heterohaloalkyl;

or, alternatively, R^{14} and R^{15} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- to 6-membered heterocycloalkyl;

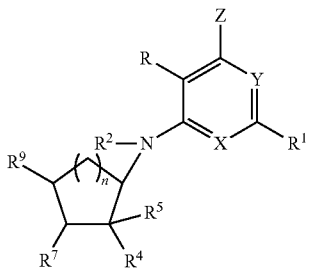
each R^{16} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl; and

each R^{17} is independently selected from alkyl, alkenyl, haloalkyl, heteroalkyl, heterohaloalkyl, —$S(O)_2$-alkyl, -alkyl-OH, —C(O)Oalkyl, —C(O)alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl;

or, alternatively, R^{16} and R^{17} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- or 6-membered heterocycloalkyl.

In one embodiment, the compounds of the invention have the structural Formula (I.a):

(I.a)



and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^4, R^5, R^7, and R^9 is selected independently and defined in Formula (I).

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and R^9 is alkyl, wherein said alkyl is unsubstituted or substituted with from one to five substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-cycloalkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, —CN, —NH_2, —NHR^{16}, and —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl.

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and R^9 is alkyl, wherein said alkyl is unsubstituted or substituted with from one to five groups independently selected from —OH, halo, —CN, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, -Oalkyl, -Ocycloalkyl, —O-alkyl-cycloalkyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, and —$S(O)_2NR^{10}R^{11}$.

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and R^9 is methyl, wherein said methyl is unsubstituted or substituted with from one to three groups independently selected from —OH, halo, alkyl, —CN, —NH_2, —NHR^{16}, —$NR^{16}R^{17}$, —$NHS(O)_2R^{10}$, —$N(R^{10})S(O)_2R^{10}$, -Oalkyl, -Ocycloalkyl, —O-alkyl-cycloalkyl, —OC(O)-alkyl, —O(C)O—NHR^{10}, —O(C)O—$N(R^{10})R^{11}$, —C(O)O-alkyl, —$S(O)_2R^{10}$, —SR^{10}, —$S(O)_2NHR^{10}$, and —$S(O)_2NR^{10}R^{11}$.

In some embodiments, in Formula (I.a), R^9 is -alkyl-$NHS(O)_2R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, in Formula (I.a), R^9 is selected from -alkyl-$N(CH_3)S(O)_2R^{10}$ and -alkyl-$N(CH_2CH_3)S(O)_2R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, in Formula (I.a), R^9 is -alkyl-O(C)O—NHR^{10}, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In some embodiments, in Formula (I.a), R^9 is selected from R^9-alkyl-O(C)O—$N(CH_3)R^{10}$ and -alkyl-O(C)O—$N(CH_2CH_3)R^{10}$, wherein R^{10} is selected from methyl, ethyl, and cyclopropyl.

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and R^9 is selected from H, —COOH, —C(O)O-alkyl, —OC(O)-alkyl, —C(O)O-aryl, —OC(O)-aryl, —C(O)O-alkyl-aryl, —OC(O)-alkyl-aryl, —C(O)O-alkyl-heteroaryl, —OC(O)-alkyl-heteroaryl, alkyl, —O-alkyl, heteroalkyl, haloalkyl, heterohaloalkyl, —O-heteroalkyl, —O-haloalkyl, —O-heterohaloalkyl, -alkyl-OH, -alkyl-OC(O)-alkyl, -alkyl-OC(O)-haloalkyl, -alkyl-NH_2, -alkyl-NHR^{16}, and -alkyl-$NR^{16}R^{17}$.

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each independently selected from H and OH; R^5 is selected from H, halo, and alkyl; and R^9 is selected from H, —CH_3, —CH_2—CH_3, —CH_2—OH, —CH_2—O-alkyl, —CH_2—OC(O)-alkyl, —CH_2—OC(O)-haloalkyl, —CH_2—NH_2, —CH_2—NHR^{16}, and —CH_2—$NR^{16}R^{17}$.

In one embodiment, in Formula (I.a), n is 1, R^2 is H, R^5 is —CH_3, and R^9 is selected from H, —CH_3, —CH_2—CH_3, —CH_2—OH, —CH_2—O-alkyl, —CH_2—$OC(O)CF_3$, —CH_2—NH_2, —CH_2—NHR^{16}, and —CH_2—$NR^{16}R^{17}$.

In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each —OH, R^5 is —CH_3, and R^9 is H.

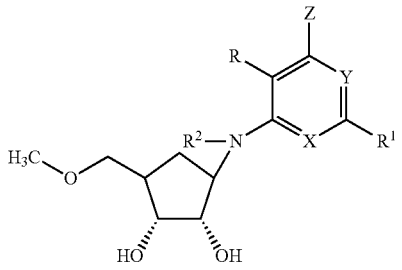
In one embodiment, in Formula (I.a), n is 1; R^2 is H; R^4 and R^7 are each —OH, R^5 is selected from H and —CH_3, and R^9 is selected from H, —OH, halo, -alkyl, -alkenyl, alkynyl, azido, aryl, heteroaryl, —O-alkyl, —O-alkenyl, —OC(O)-alkyl, —SH, —S-alkyl, —NH_2, —NO_2, —NHR^{10}, —$NR^{10}R^{11}$, —C(O)OH, —C(O)OR^{10}, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —S(O)NHR^{10}, —S(O)$NR^{10}R^{11}$, —S(O)R^{10}, —$S(O)_2NHR^{10}$, —$S(O)_2NR^{10}R^{11}$, and —$S(O)_2R^{10}$,

wherein each of said -alkyl, said -alkenyl, said alkynyl, said aryl, said heteroaryl, said —O-alkyl, said —O-alkenyl, said —OC(O)-alkyl, and said —S-alkyl is unsubstituted or optionally independently substituted with from one to three substituents, which can be the same or different, each substituent being independently selected from halo, —OH, alkyl, haloalkyl, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-alkenyl, —O-haloalkyl, —O-haloalkenyl, —OC(O)-alkyl, —OC(O)-alkenyl, —OC(O)-haloalkyl, —OC(O)-haloalkenyl, —C(O)O-alkyl, —C(O)O-alkenyl, —C(O)O-haloalkyl, —C(O)O-haloalkenyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl.

In one embodiment, in Formula (I.a), X is N, Y is N, n is 1; R^2 is H; R^4 and R^7 are each —OH, R^5 is selected from H and $—CH_3$, and R^9 is selected from H, -alkyl, -alkyl-OH, -alkyl-$S(O)_2$alkyl, -alkyl-S-alkyl, haloalkyl, heteroalkyl, -alkyl-CN, -alkyl-NH_2, -alkyl-NHR^{16}, and -alkyl-$N(alkyl)_2$. In one such embodiment, each said alkyl is selected from straight or branched lower alkyl.

In one embodiment, the compounds of the invention have the structural Formula (I.a.1):

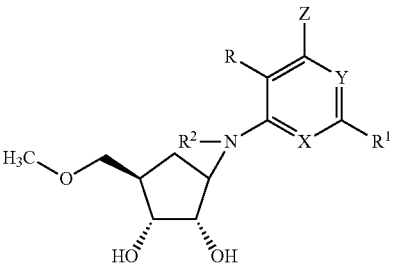
(I.a.1)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.1.i):

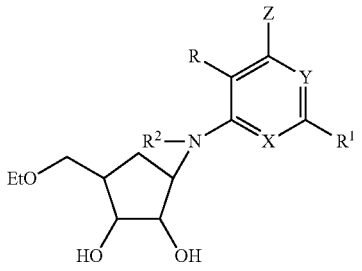
(I.a.1.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.2):

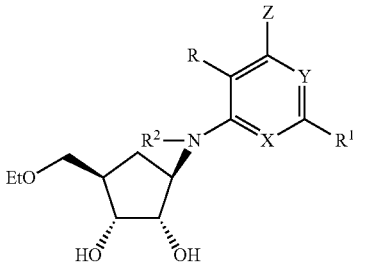
(I.a.2)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.2.i):

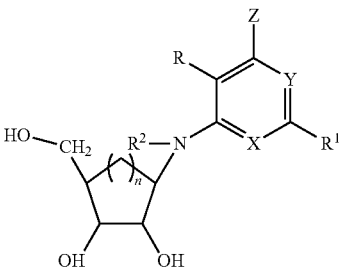
(I.a.2.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.3):

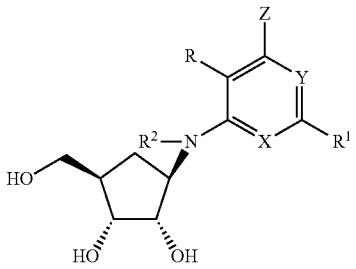
(I.a.3)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.3.i)

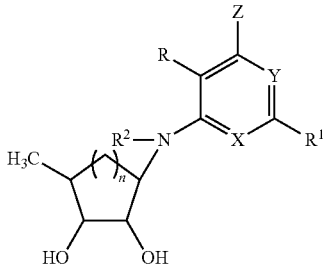
(I.a.3.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.4):

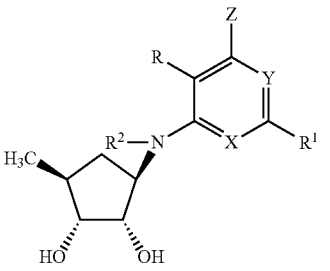
(I.a.4)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.4.i):

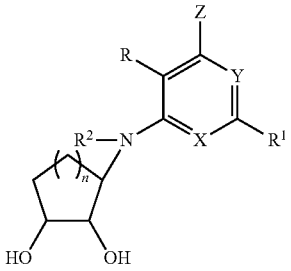
(I.a.4.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.5):

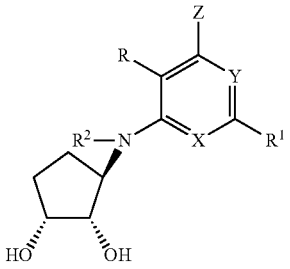
(I.a.5)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.5.i):

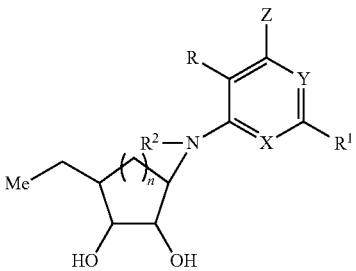
(I.a.5.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.6):

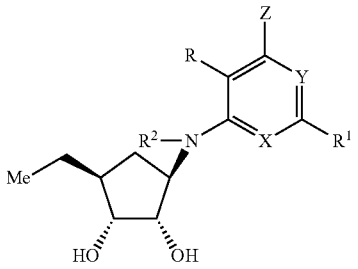
(I.a.6)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.6.i):

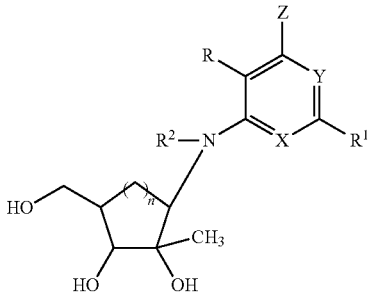
(I.a.6.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.7):

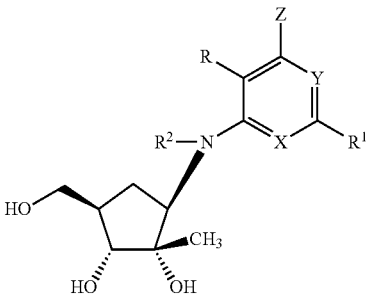
(I.a.7)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.7.i):

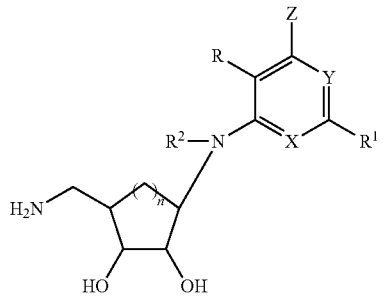
(I.a.7.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.8):

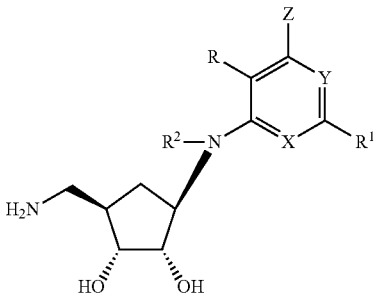
(I.a.8)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.8.i):

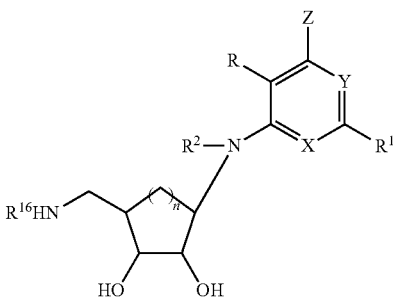
(I.a.8.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.9):

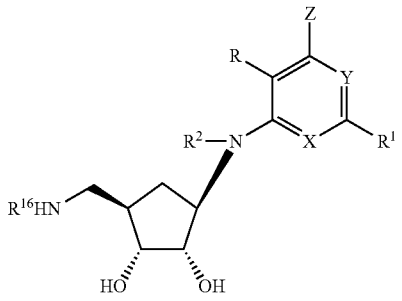
(I.a.9)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, n, and R^{16} is selected independently defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.9.i):

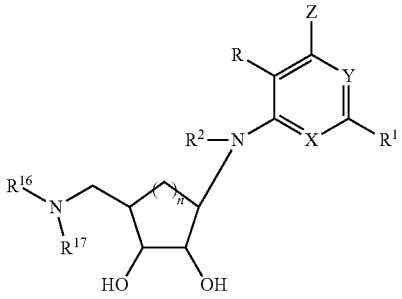
(I.a.9.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and R^{16} is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.10):

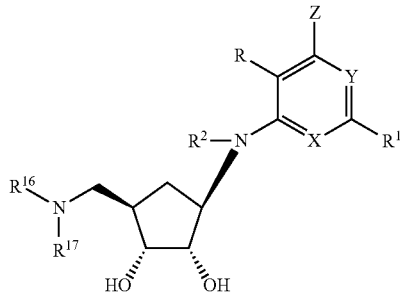
(I.a.10)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, n, R^{16}, and R^{17} is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.10.i):

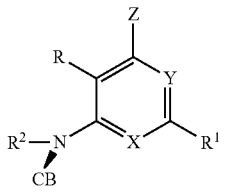
(I.a.10.i)



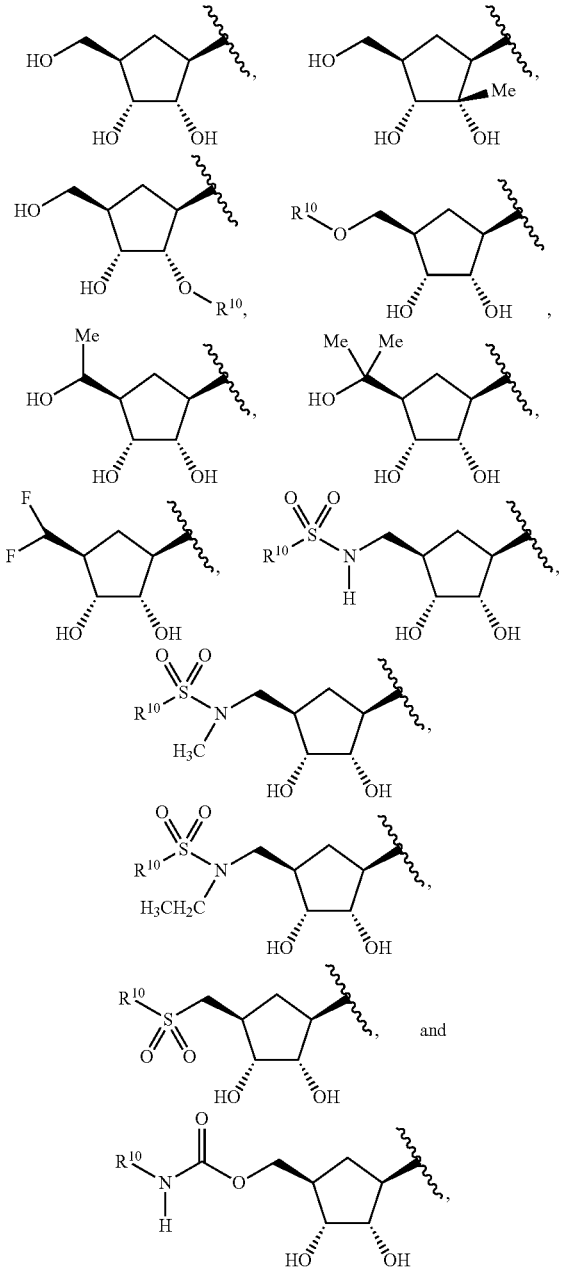
and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^{16}, and R^{17} is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.a.10.j):

(I.a.10.j)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and is selected independently and defined in Formula (I), and wherein CB is a moiety selected from the group consisting of:



and

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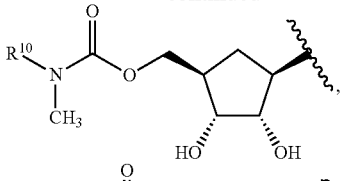
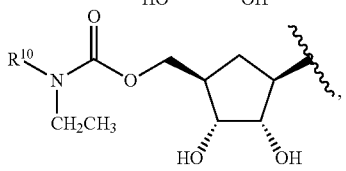


and



wherein each R^{10} is independently selected from the group consisting of methyl, ethyl, and cyclopropyl.

In one embodiment, in Formula (I.a.10.j):

X is N;

Y is N;

R^2 is H;

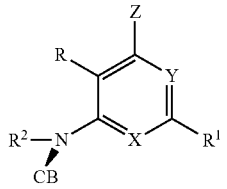
Z is selected from the group consisting of H, methyl, cyclopropyl, and chloro;

R is as defined in Formula (I); and

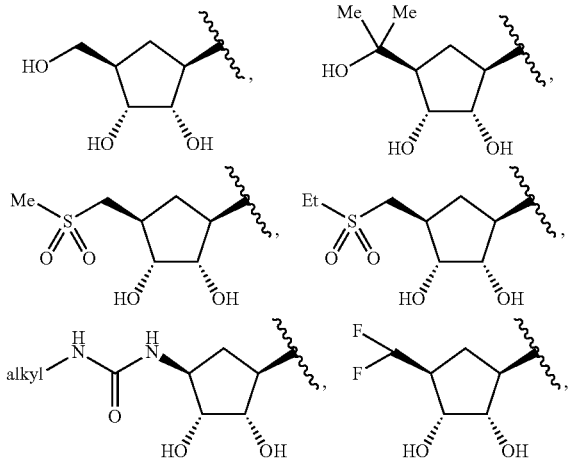
R^1 is as defined in Formula (I), or, alternatively, as in the various other embodiments described herein, or, alternatively, as in the examples. In one such embodiment, R^1 is selected from the group consisting of —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$.

In one embodiment, the compounds of the invention have the structural Formula (I.a.10.k):

(I.a.10.k)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and is selected independently and defined in Formula (I), and wherein CB is a moiety selected from the group consisting of:



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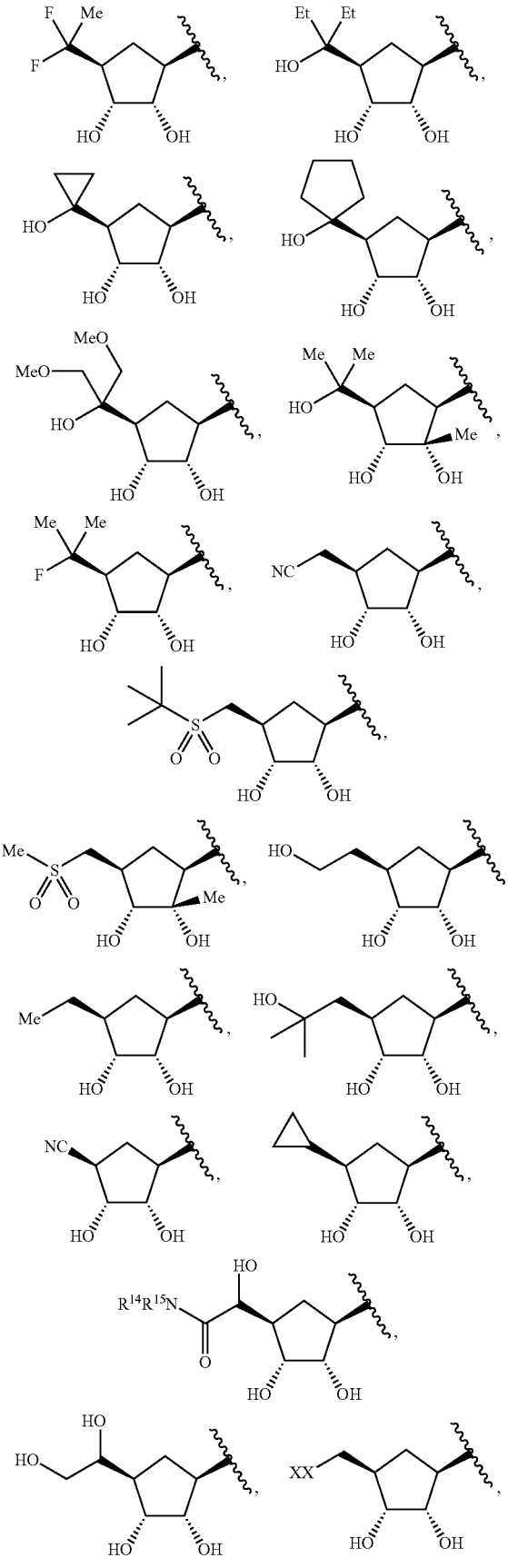

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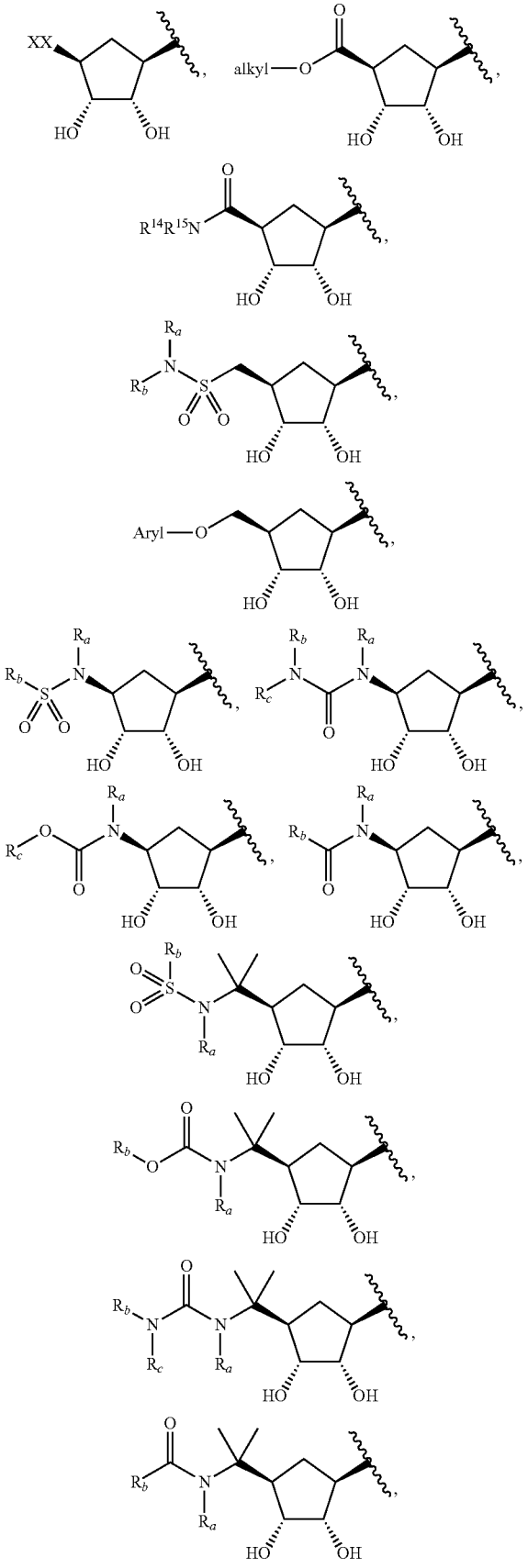

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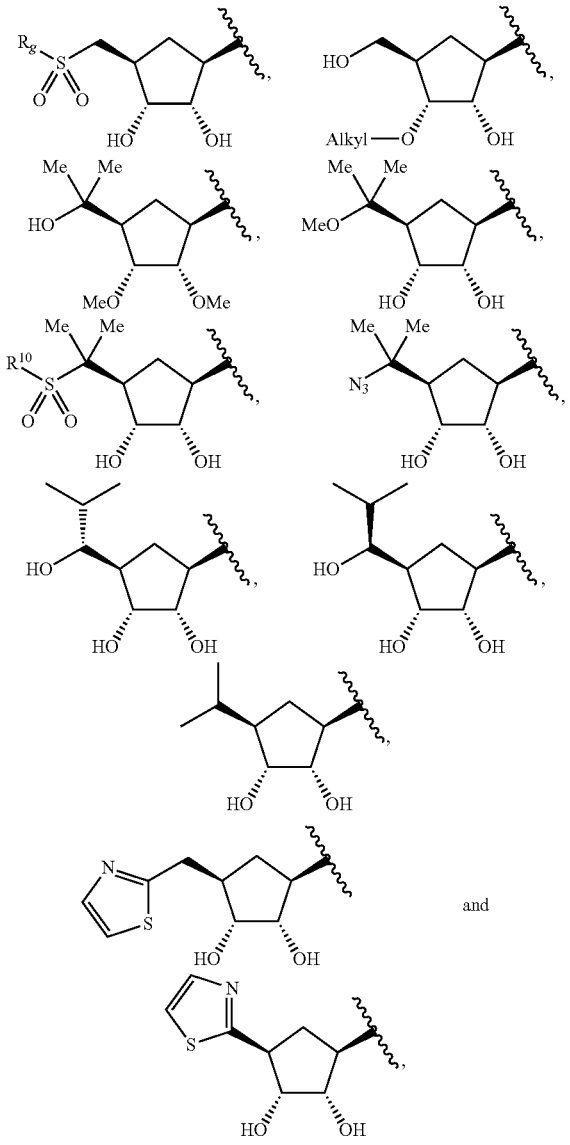
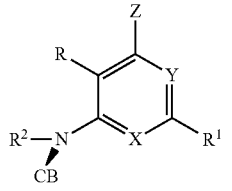


and

wherein XX (when present) is selected from the group consisting of aryl and heteroaryl, and R^{14}, R^{15}, R^a, R^b, and R^c (when present) are each independently as defined in Formula (I), and R^g (when present) is selected from the group consisting of aryl and heteroaryl.

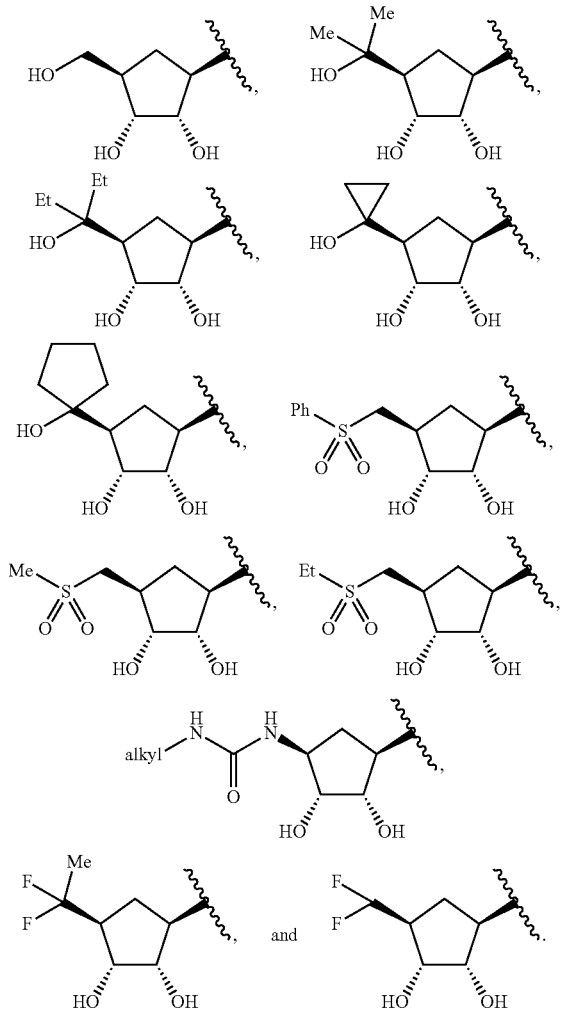
In one embodiment, the compounds of the invention have the structural Formula (I.a.10.L):

(I.a.10.L)



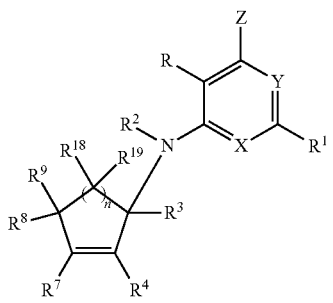
and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1,

X, Y, Z, and is selected independently and defined in Formula (I), and wherein CB is a moiety selected from the group consisting of:



In one embodiment, the compounds of the invention have the structural Formula (I.B):

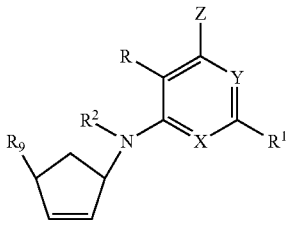
(I.B)



and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^4, R^7, R^8, R^9, R^{18}, R^{19}, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.b):

(I.b)



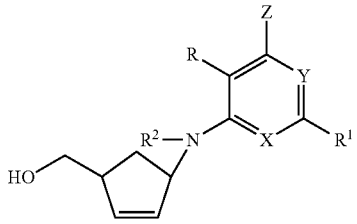
and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and R^9 is selected independently and defined in Formula (I).

In one embodiment, in Formula (I.b), R^2 is H, and R^9 is selected from H, —CH_3, —CH_2—O-alkyl, —CH_2—OH, —CH_2—OC(O)-alkyl, —CH_2—OC(O)-haloalkyl, —CH_2—CH_3,—CH_2—NH_2, —CH_2—NHR^{16}, and —CH_2—$NR^{16}R^{17}$.

In one embodiment, in Formula (I.b), R^2 is H, and R^9 is selected from —CH_2—O-alkyl, and —CH_2—OH.

In one embodiment, the compounds of the invention have the structural Formula (I.b.1):

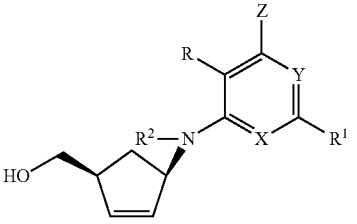
(I.b.1)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.b.1.i):

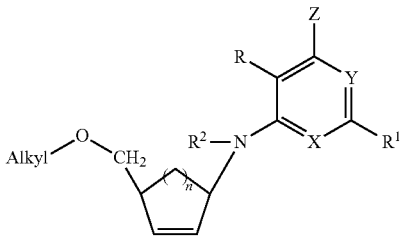
(I.b.1.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.b.2):

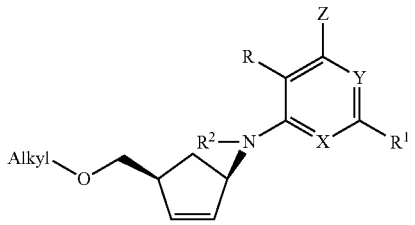
(I.b.2)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the Formula (I.b.2.i):

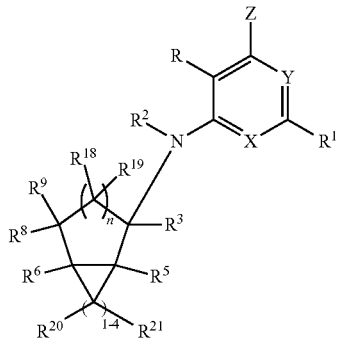
(I.b.2.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.C):

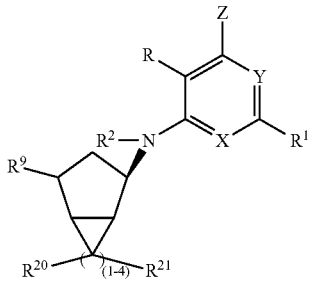
(I.C)



and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^5, R^6, R^8, R^9, R^{18}, R^{19}, R^{20}, R^{21}, and n is selected independently and defined in Formula (I), with the proviso that R^5 and R^6 are not taken together to form a double bond.

In one embodiment, the compounds of the invention have the structural Formula (I.c):

(I.c)

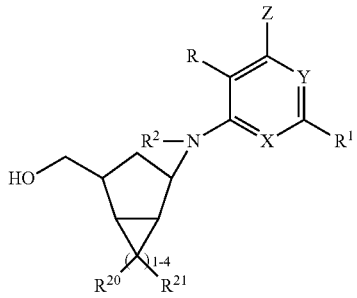


and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^9, R^{20}, and R^{21} is selected independently and defined in Formula (I).

In one embodiment, in Formula (I.c), R^2 is H; R^9 is selected from H, —CH_3, —CH_2—O-alkyl, —CH_2—OH, —CH_2—OC(O)-alkyl, —CH_2—OC(O)-haloalkyl, —CH_2—CH_3, —CH_2—NH_2, —CH_2—NHR^{16}, and —CH_2—$NR^{16}R^{17}$; and each of R^{20} and R^{21} is independently selected from H and —CH_3.

In one embodiment, the compounds of the invention have the structural Formula (I.c.1):

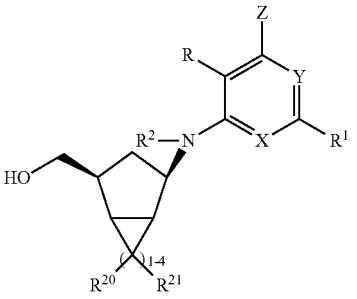
(I.c.1)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.c.1.i):

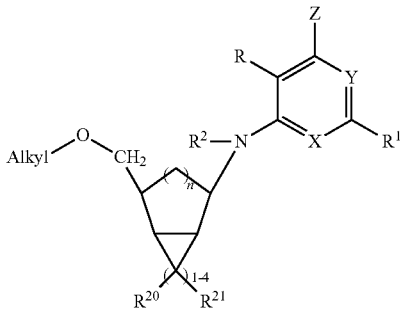
(I.c.1.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.c.2):

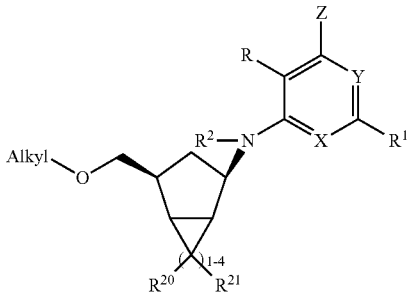
(I.c.2)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.c.2.i):

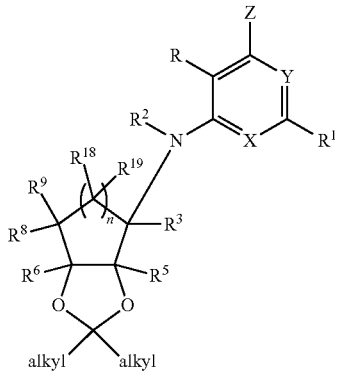
(I.c.2.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.D):

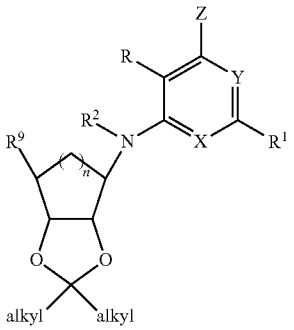
(I.D)



and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^5, R^6, R^8, R^9, R^{18}, and R^{19}, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.d):

(I.d)



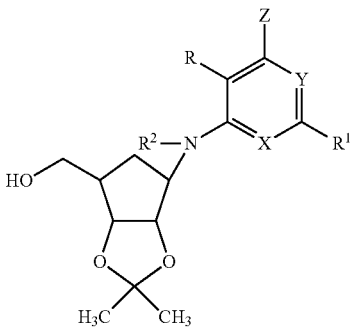
and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^9, and n is selected independently and defined in Formula (I).

In one embodiment, in Formula (I.d), n is 1 and R^9 is selected from H, $—CH_3$, $—CH_2—$O-alkyl, $—CH_2—OH$, $—CH_2—OC(O)$-alkyl, $—CH_2—OC(O)$-haloalkyl, $—CH_2—CH_3$, $—CH_2—NH_2$, $—CH_2—NHR^{16}$, and $—CH_2—NR^{16}R^{17}$.

In one embodiment, in Formula (I.d), n is 1 and R^9 is selected from $—CH_2—$O-alkyl, and $—CH_2—OH$.

In one embodiment, the compounds of the invention have the structural Formula (I.d.1):

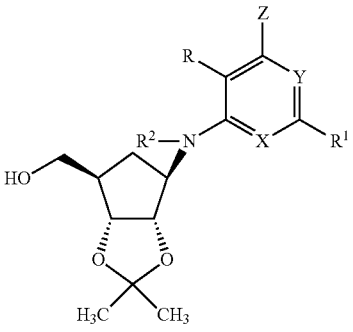
(I.d.1)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.d.1.i):

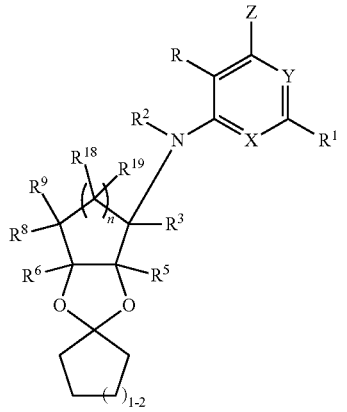
(I.d.1.i)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, and R^2 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (I.E):

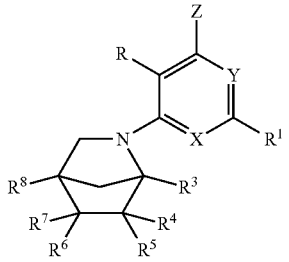
(I.E)



and includes pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^2, R^3, R^5, R^6, R^8, R^9, R^{18}, and R^{19}, and n is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (II):

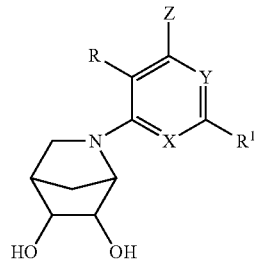
(II)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, Z, R^3, R^4, R^5, R^6, R^7, and R^8 is selected independently and defined in Formula (I).

In one embodiment, the compounds of the invention have the structural Formula (II):

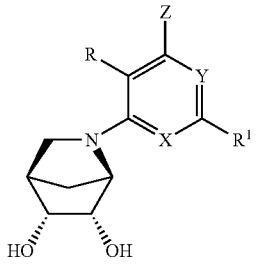
(II.A)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, and Z is selected independently and wherein R, R^1, X, Y, and Z are defined in Formula (I).

In one embodiment, in Formula (I), the compounds of the invention have the structural Formula (II.a.1):

(II.A.1)



and include pharmaceutically acceptable salts, esters, prodrugs, or isomers of said compounds, wherein each of R, R^1, X, Y, and Z is selected independently and wherein R, R^1, X, Y, and Z are defined in Formula (I).

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), X is N and Y is N.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), X is N and Y is CH.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), X is CH and Y is N.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is selected from the group consisting of halo, alkyl, haloalkyl, cycloalkyl, and $—NH_2$. Non-limiting examples of Z when Z is cycloalkyl include cyclopropyl. Non-limiting examples of Z when Z is haloalkyl include fluoroalkyl (up to perfluoroalkyl).

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is selected from the group consisting of halo, alkyl, and cycloalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C),

(I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is selected from the group consisting of H, alkyl, halo, and cyclopropyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is selected from the group consisting of H, methyl, and chloro.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is H.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is halo.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —Cl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —F.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —OH.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —SH.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —Salkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —S—CH_3.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is -alkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —CH_3.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —CH_2CH_3.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —Oalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —OCH_3.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is -haloalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —CF_3.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —CHF_2.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is —CH_2F.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k),

(I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is cycloalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is cyclopropyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is aryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is phenyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-thiophenyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 3-thiophenyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-thiazolyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-oxazolyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-pyrimidinyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-pyridyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-pyrazinyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is 2-imidazolyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is $—NH_2$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is $—NHR^{12}$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is $—NR^{12}R^{13}$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is selected from the group consisting of Cl and methyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is selected from the group consisting of $—NH_2$, $—NHR^{14}$, and $—NR^{14}R^{15}$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is selected from the group consisting of $—NH_2$ and $—NHR^{14}$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is H.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is halo.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is Cl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is F.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is alkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is $—CH_3$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is $—CH_2CH_3$.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is heteroalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —OH.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —O-alkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —O-aryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —O-heteroalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —O-heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —SH.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —S-alkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —S-aryl.

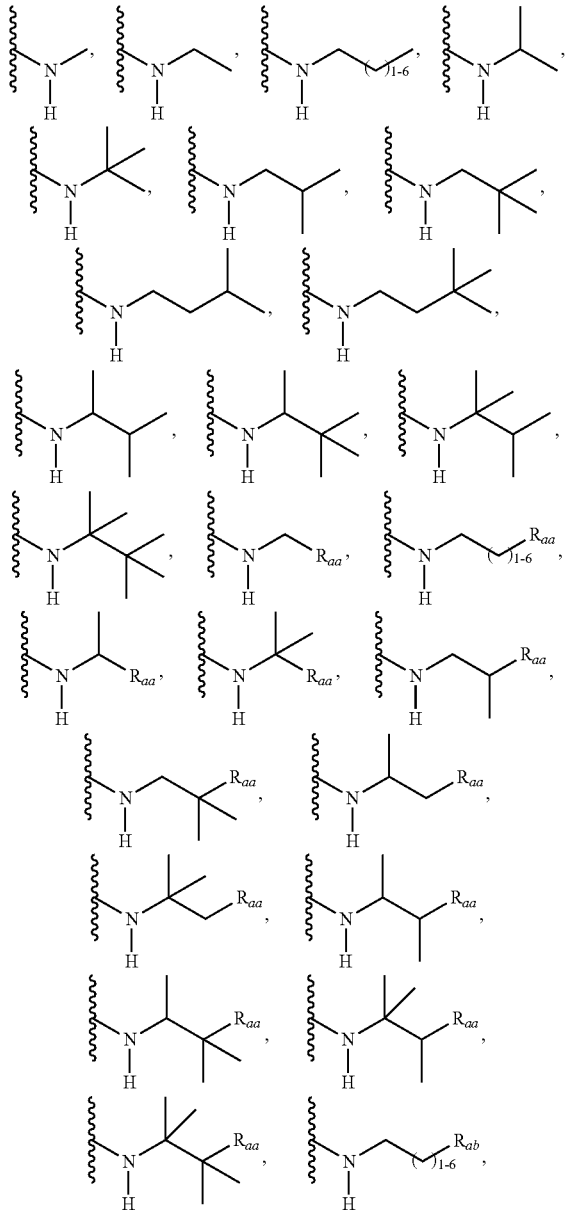
In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —S-heteroalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C),

(I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —S-heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —NH_2.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —NHR^{14}. Non-limiting examples of R^1 when R^1 is —NHR^{14} include:



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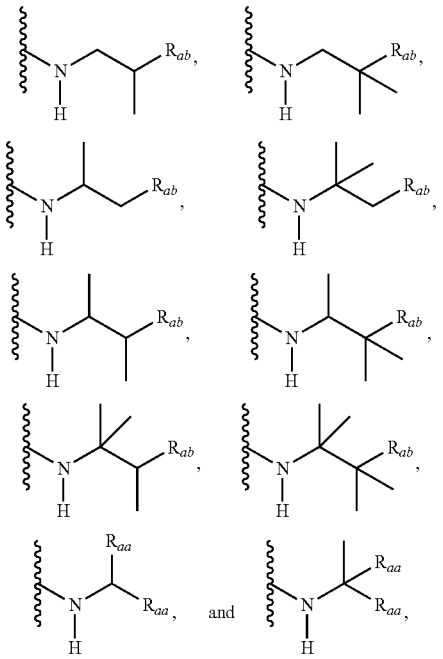
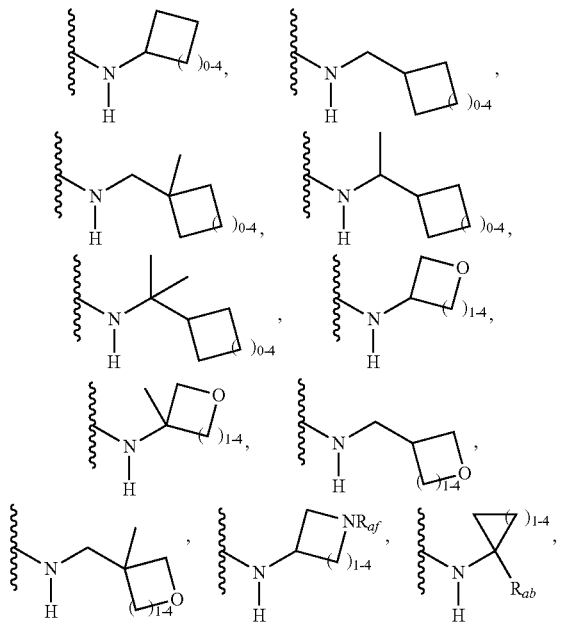


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each R_{aa} is independently selected from haloalkyl (non-limiting examples of which include —CH_2F, —CHF_2, —CF_3, etc.), R_{ab} is selected from OH, OAc, and —O-alkyl (non-limiting examples of which include —O-Me, —O-Et, —O-n-Pr, —O-i-Pr, —O-n-Bu, —O-i-Bu, and —O-t-Bu), —O-haloalkyl (non-limiting examples of which include —O—CH_2F, —O—CHF_2, and —O—CF_3), —NH_2, —NHalkyl, and N(alkyl)$_2$.

Additional non-limiting examples of R^1 when R^1 is —NHR^{14} include:



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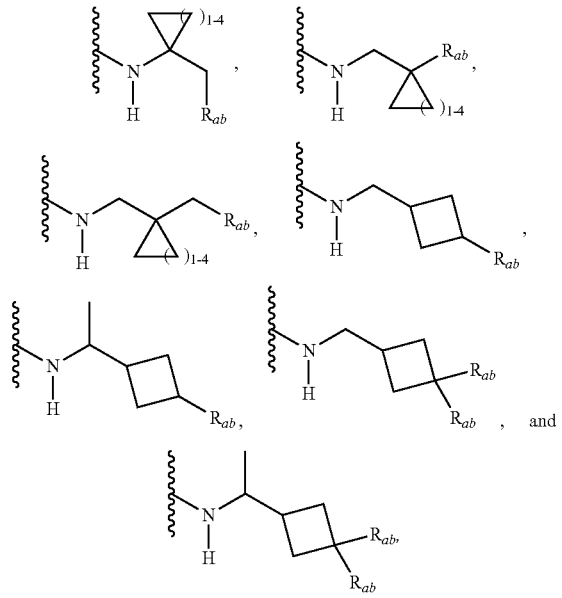
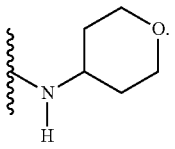
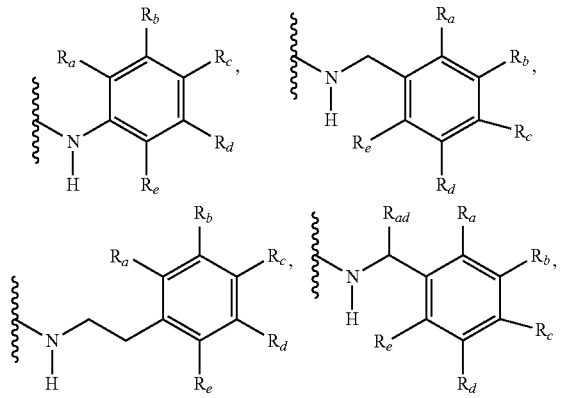


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein R_{af} is selected from the group consisting of H and acetyl, and each R_{ab} is independently selected from the group consisting of OH, OAc, —Oalkyl, O-haloalkyl, halo, haloalkyl, alkyl, cycloalkyl, aryl, heteroaryl, —O-aryl, —S-aryl, —S-alkyl, —SO2-alkyl, —CO2-alkyl, —CO2H, and amino.

It shall be understood that positional isomers of the heteroatoms shown in the moieties above are also contemplated. Such positional isomers include symmetric positional isomers such as



Additional non-limiting examples of R^1 when R^1 is —NHR^{14} include:



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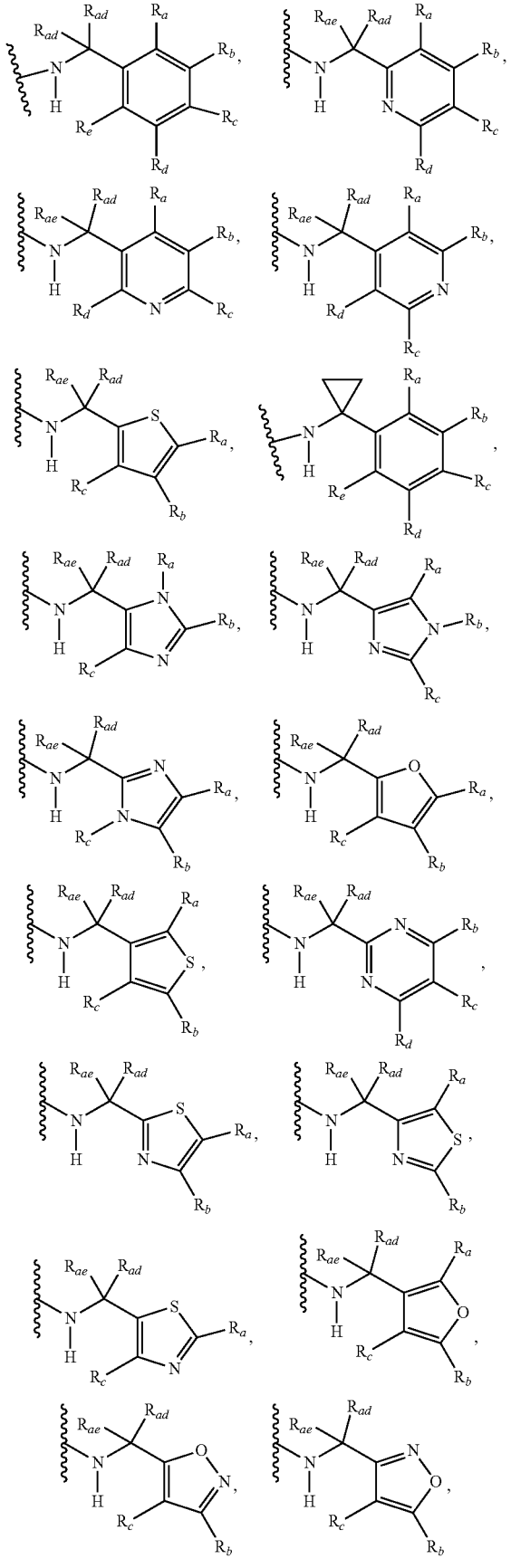

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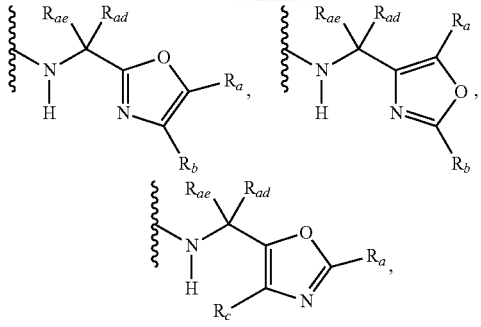
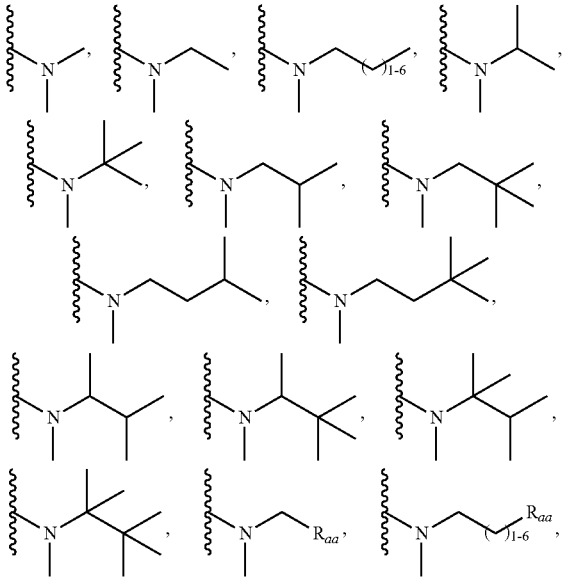


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each of R_a, R_b, R_c, R_d, and R_e, is independently selected from H, halo, —OH, —CN, alkyl, haloalkyl, -alkyl-OH, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-haloalkyl, —O-alkyl-OH, aryl, —O-aryl, —S-aryl, —O-alkyl-aryl, —S-alkyl-aryl, heteroaryl, —O-heteroaryl, —S-heteroaryl, —O-alkyl-heteroaryl, —S-alkyl-heteroaryl, heterocycloalkyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)H, —C(O)OH, —C(O)O-alkyl, —OC(O)-alkyl, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —C(O)ONH_2, —C(O)$ONHR^{10}$, —C(O)$ONR^{10}R^{11}$, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —NO_2, substituted aryl, and substituted heteroaryl, wherein each of said substituted aryl and said substituted heteroaryl independently contains from one to three substituents, which may be the same or different, each substituent being independently selected from halo, alkyl, —O-alkyl, and —C(O)Oalkyl, and wherein each R_{ad} and each R_{ae} is independently selected from alkyl and haloalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —$NR^{14}R^{15}$. Non-limiting examples of R^1 when R^1 is —$NR^{14}R^{15}$ include:



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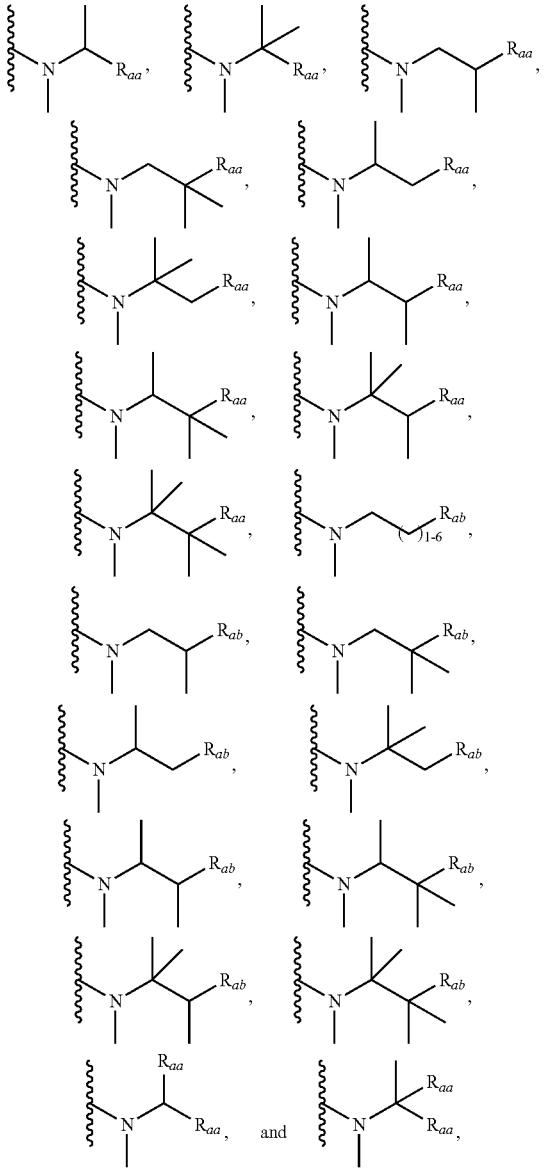
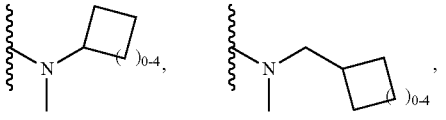


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each R_{aa} is independently selected from haloalkyl (non-limiting examples of which include —CH_2F, —CHF_2, —CF_3, etc.), R_{ab} is selected from OH, OAc, and —O-alkyl (non-limiting examples of which include —O-Me, —O-Et, —O-n-Pr, —O-i-Pr, —O-n-Bu, —O-i-Bu, and —O-t-Bu), —O-haloalkyl (non-limiting examples of which include —O—CH_2F, —O—CHF_2, and —O—CF_3), —NH_2, —NHalkyl, and N(alkyl)$_2$.

Additional non-limiting examples of R^1 when R^1 is —$NR^{14}R^{15}$ include:



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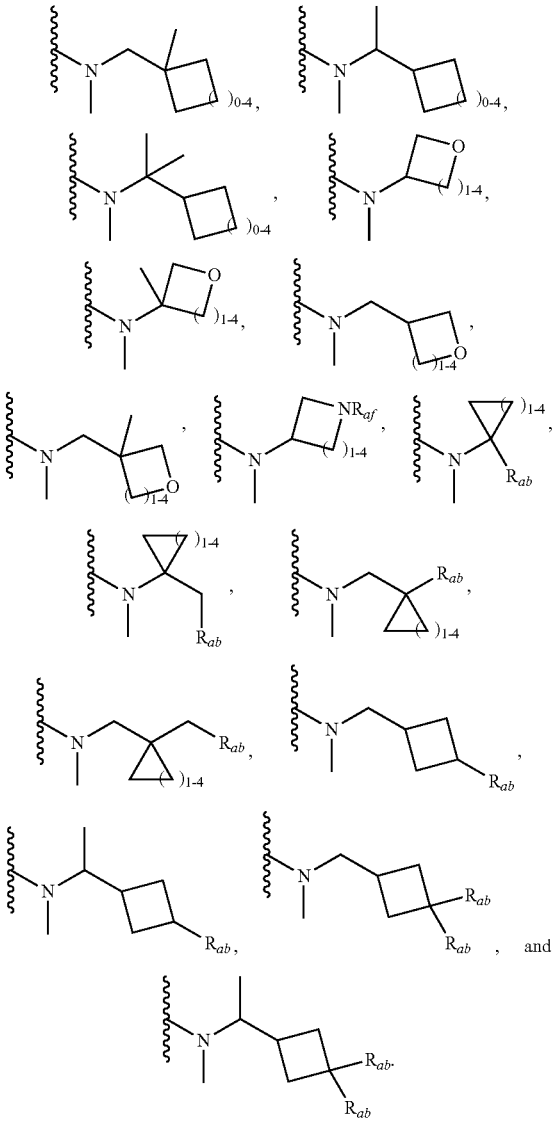
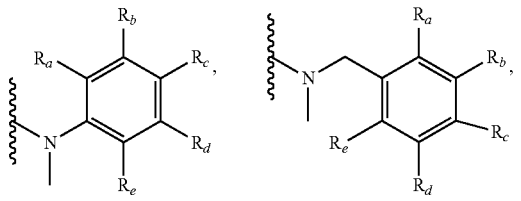


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein R_{af} is selected from the group consisting of H and acetyl, and each R_{ab} is independently selected from the group consisting of OH, OAc, —Oalkyl, O-haloalkyl, halo, haloalkyl, alkyl, cycloalkyl, aryl, heteroaryl, —O-aryl, —S-aryl, —S-alkyl, —SO2-alkyl, —CO2-alkyl, —CO2H, and amino.

Additional non-limiting examples of R^1 when R^1 is $—NR^{14}R^{15}$ include:



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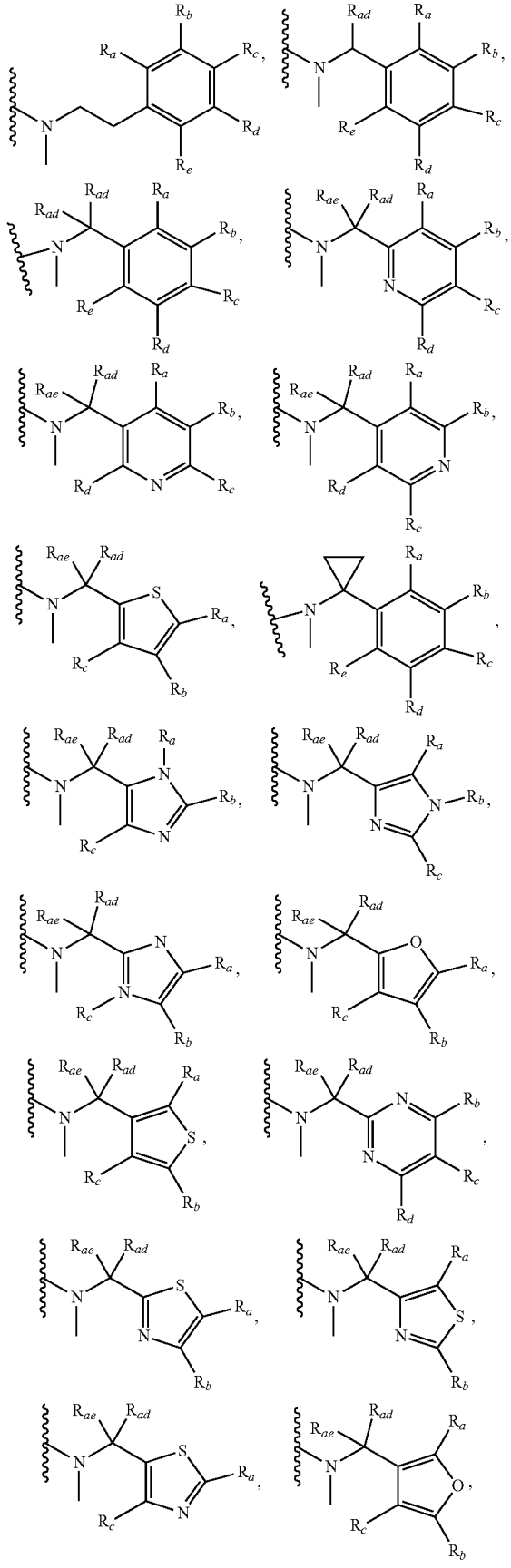

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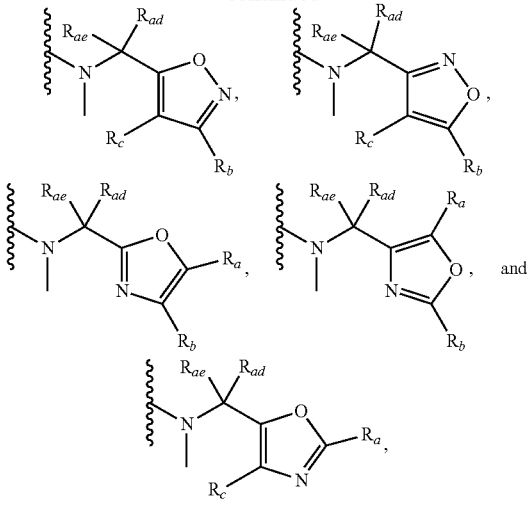
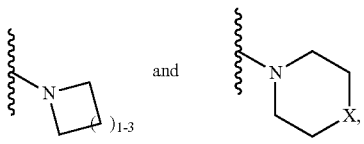


and

wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each of R_a, R_b, R_c, R_d, and R_e, is independently selected from H, halo, —OH, —CN, alkyl, haloalkyl, -alkyl-OH, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-haloalkyl, —O-alkyl-OH, aryl, —O-aryl, —S-aryl, —O-alkyl-aryl, —S-alkyl-aryl, heteroaryl, —O-heteroaryl, —S-heteroaryl, —O-alkyl-heteroaryl, —S-alkyl-heteroaryl, heterocycloalkyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)H, —C(O)OH, —C(O)O-alkyl, —OC(O)-alkyl, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —C(O)ONH_2, —C(O)$ONHR^{10}$, —C(O)$ONR^{10}R^{11}$, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —NO_2, substituted aryl, and substituted heteroaryl, wherein each of said substituted aryl and said substituted heteroaryl independently contains from one to three substituents, which may be the same or different, each substituent being independently selected from halo, alkyl, —O-alkyl, and —C(O)Oalkyl, and wherein each R_{ad} and each R_{ae} is independently selected from alkyl and haloalkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), R^1 is —$NR^{14}R^{15}$, wherein R^{14} and R^{15} are linked together with the nitrogen to which they are attached to form an unsubstituted or substituted 4- to 6-membered heterocycloalkyl. Non-limiting examples of R^1 when R^1 is —$NR^{14}R^{15}$ and R^{14} and R^{15} are so linked include:



and

wherein X is selected from O, NH, and NMe.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is halo; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is as defined in claim **1**.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is heteroaryl; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is as defined in claim **1**.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is H; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is as defined in claim **1**.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is alkyl; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is as defined in claim **1**.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is halo; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is heteroaryl; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is H; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), Z is alkyl; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R is heteroaryl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1), X and Y are each N; R is selected from unsubstituted aryl, substituted aryl, unsubstituted heteroaryl, and substituted heteroaryl, wherein said substituents, when present, are defined in Formula (I); Z is selected from halo, —OH, —SH, alkyl, —NH_2, —NHR^{12}, and —$NR^{12}R^{13}$; R^1 is selected from —NH_2, —NHR^{14}, and —$NR^{14}R^{15}$; and R^2 is selected from H and alkyl.

In other embodiments, in each of Formulas (I), (I.A), (I.a), (I.a.1), (I.a.1.i), (I.a.2), (I.a.2.i), (I.a.3), (I.a.3.i), (I.a.4), (I.a.4.i), (I.a.5), (I.a.5.i), (I.a.6), (I.a.6.i), (I.a.7), (I.a.7.i), (I.a.8), (I.a.8.i), (I.a.10), (I.a.10.i), (I.a.10.j), (I.a.10.k), (I.a.10.L), (I.B), (I.b), (I.b.1), (I.b.1.i), (I.b.2), (I.b.2.i), (I.C), (I.c), (I.c.1), (I.c.1.i), (I.c.2), (I.c.2.i), (I.D), (I.d), (I.d.1), (I.d.1.i), (I.E), (II), (II.A), and (II.A.1):

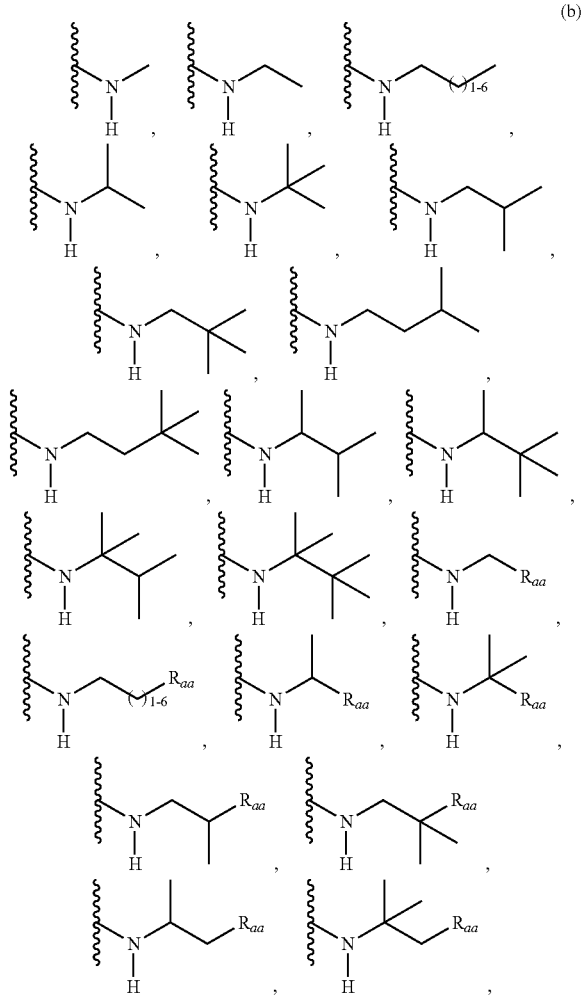
X is N;

Y is N;

R^1 is selected from the group consisting of:

(a) —NH_2,

(b)



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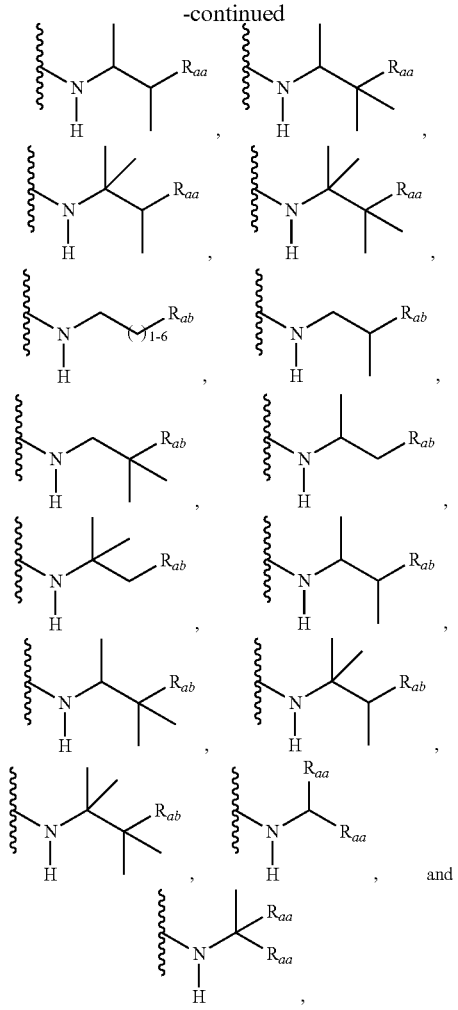
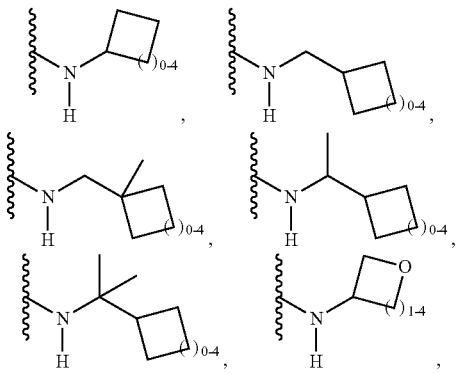


and

wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each R_{aa} is independently selected from haloalkyl (non-limiting examples of which include —CH_2F, —CHF_2, —CF_3, etc.), R_{ab} is selected from OH, OAc, and —O-alkyl (non-limiting examples of which include —O-Me, —O-Et, —O-n-Pr, —O-i-Pr, —O-n-Bu, —O-i-Bu, and —O-t-Bu), —O-haloalkyl (non-limiting examples of which include —O—CH_2F, —O—CHF_2, and —O—CF_3), —NH_2, —NHalkyl, and N(alkyl)$_2$,



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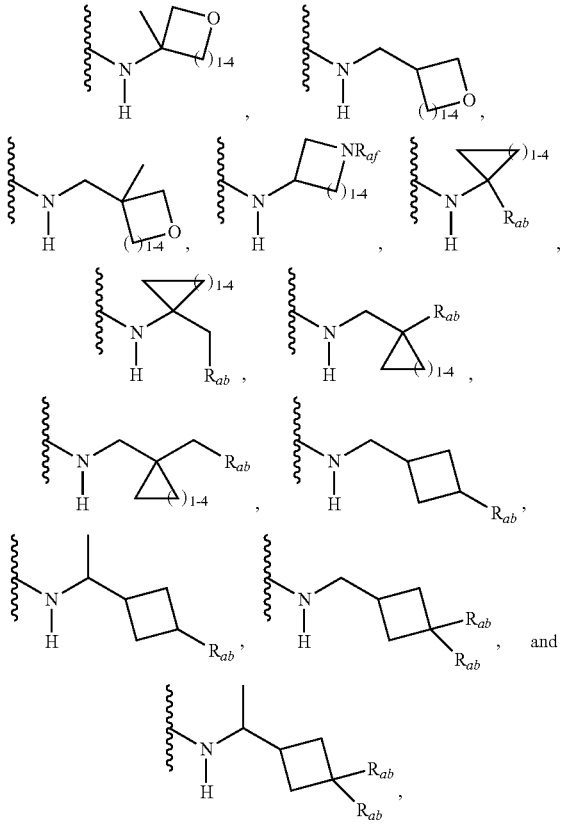
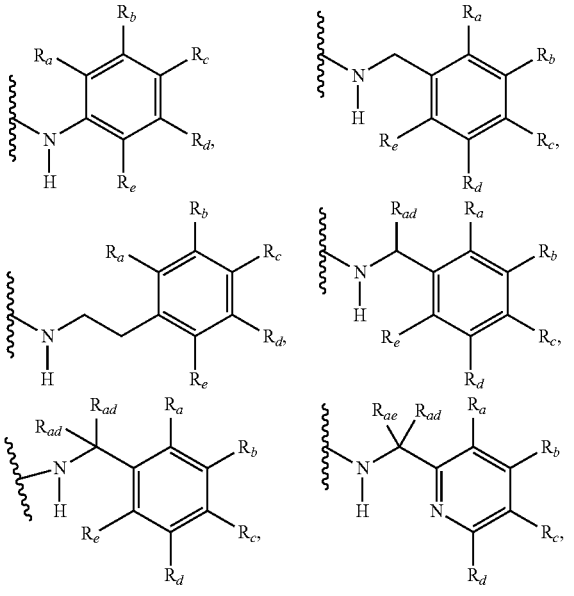


wherein R_{af} is selected from the group consisting of H and acetyl, and each R_{ab} is independently selected from the group consisting of OH, OAc, -Oalkyl, O-haloalkyl, halo, haloalkyl, alkyl, cycloalkyl, aryl, heteroaryl, —O-aryl, —S-aryl, —S-alkyl, —SO2-alkyl, —CO2-alkyl, —CO2H, and amino;

(d)



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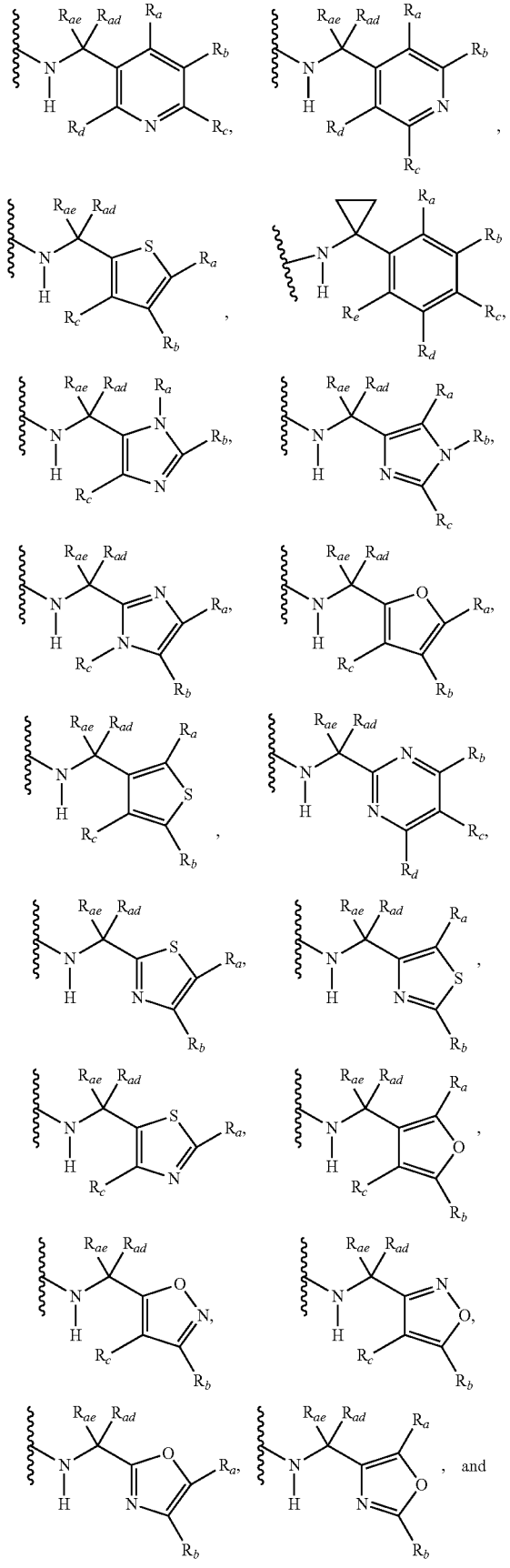

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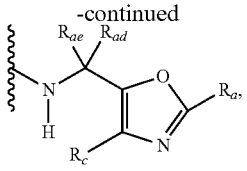
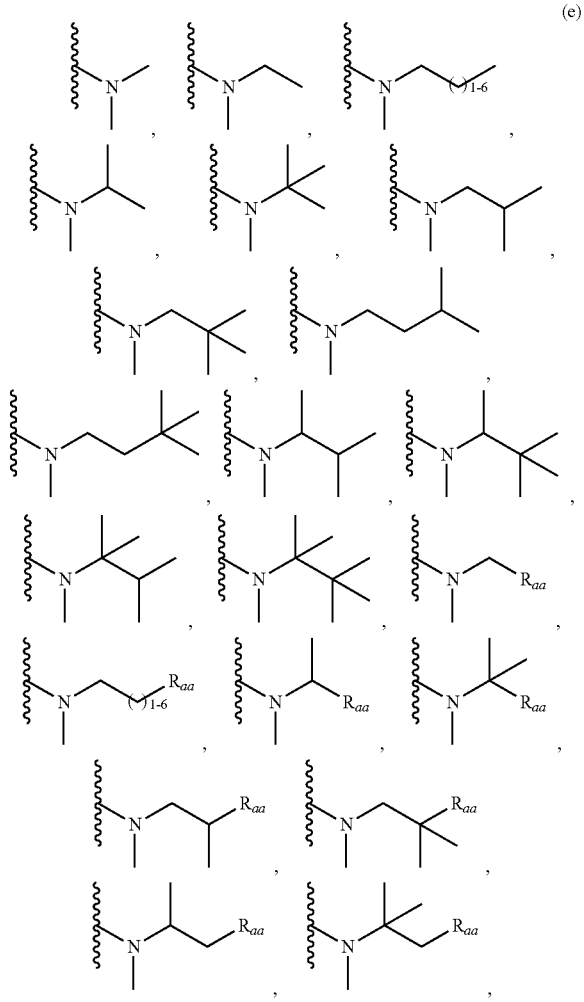


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each of R_a, R_b, R_c, R_d, and R_e, is independently selected from H, halo, —OH, —CN, alkyl, cycloalkyl, haloalkyl, -alkyl-OH, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-haloalkyl, —O-alkyl-OH, aryl, —O-aryl, —S-aryl, —O-alkyl-aryl, —S-alkyl-aryl, heteroaryl, —O-heteroaryl, —S-heteroaryl, —O-alkyl-heteroaryl, —S-alkyl-heteroaryl, heterocycloalkyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)H, —C(O)OH, —C(O)O-alkyl, —OC(O)-alkyl, —$C(O)NH_2$, —$C(O)NHR^{10}$, —$C(O)NR^{10}R^{11}$, —$C(O)ONH_2$, —$C(O)ONHR^{10}$, —$C(O)ONR^{10}R^{11}$, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —NO_2, substituted aryl, and substituted heteroaryl, wherein each of said substituted aryl and said substituted heteroaryl independently contains from one to three substituents, which may be the same or different, each substituent being independently selected from halo, alkyl, —O-alkyl, and —C(O)Oalkyl, and wherein each R_{ad} is independently selected from alkyl and haloalkyl,

(e)



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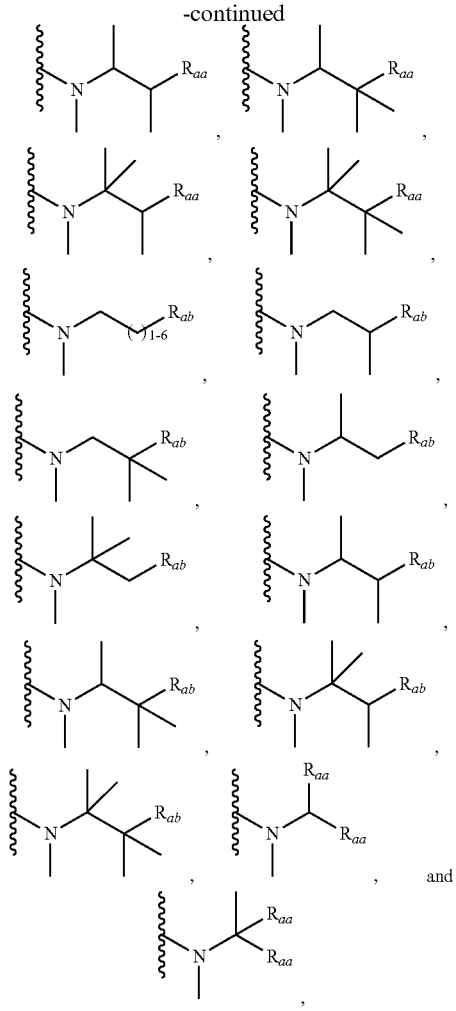
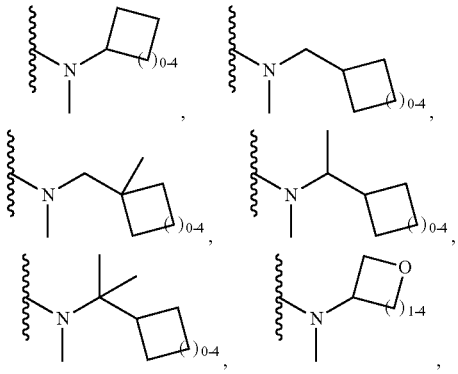


and

wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each R_{aa} is independently selected from haloalkyl (non-limiting examples of which include —CH_2F, —CHF_2, —CF_3, etc.), R_{ab} is selected from OH, OAc, and —O-alkyl (non-limiting examples of which include —O-Me, —O-Et, —O-n-Pr, —O-i-Pr, —O-n-Bu, —O-i-Bu, and —O-t-Bu), —O-haloalkyl (non-limiting examples of which include —O—CH_2F, —O—CHF_2, and —O—CF_3), —NH_2, —NHalkyl, and $N(alkyl)_2$,

(f)



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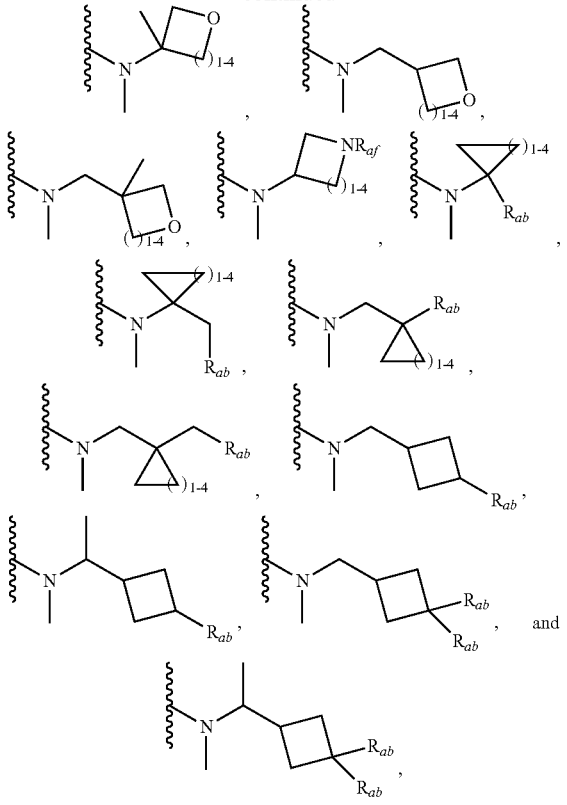
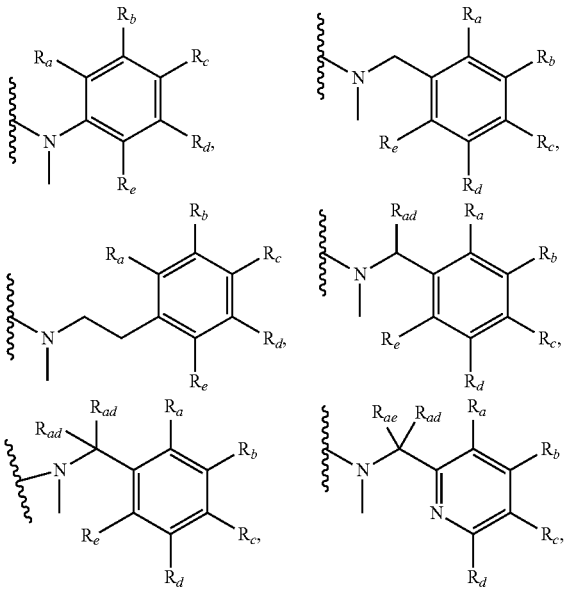


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein R_{af} is selected from the group consisting of H and acetyl, and each R_{ab} is independently selected from the group consisting of OH, OAc, —Oalkyl, O-haloalkyl, halo, haloalkyl, alkyl, cycloalkyl, aryl, heteroaryl, —O-aryl, —S-aryl, —S-alkyl, —SO2-alkyl, —CO2-alkyl, —CO2H, and amino;

(g)



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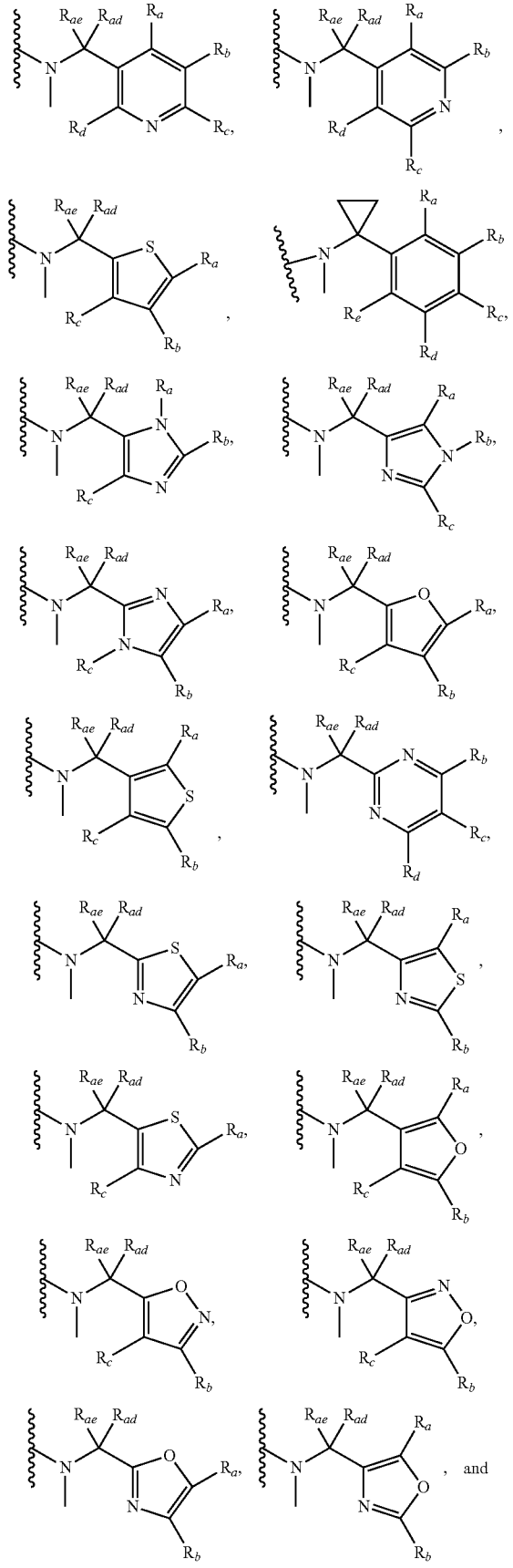

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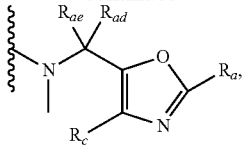
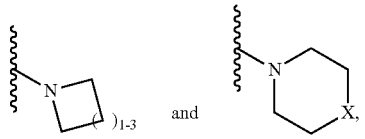


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each of R_a, R_b, R_c, R_d, and R_e, is independently selected from H, halo, —OH, —CN, alkyl, haloalkyl, -alkyl-OH, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-haloalkyl, —O-alkyl-OH, aryl, —O-aryl, —S-aryl, —O-alkyl-aryl, —S-alkyl-aryl, heteroaryl, —O-heteroaryl, —S-heteroaryl, —O-alkyl-heteroaryl, —S-alkyl-heteroaryl, heterocycloalkyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)H, —C(O)OH, —C(O)O-alkyl, —OC(O)-alkyl, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —C(O)ONH_2, —C(O)$ONHR^{10}$, —C(O)$ONR^{10}R^{11}$, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —NO_2, substituted aryl, and substituted heteroaryl, wherein each of said substituted aryl and said substituted heteroaryl independently contains from one to three substituents, which may be the same or different, each substituent being independently selected from halo, alkyl, —O-alkyl, and —C(O)Oalkyl, and wherein each R_{ad} is independently selected from alkyl and haloalkyl, and

(h)



wherein X is selected from O, NH, and NMe; and

Z is selected from the group consisting of H, halo, —OH, —SH, —CN, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, heterohaloalkyl, —S-alkyl, —O-alkyl, —O-aryl, —O-heteroaryl, cycloalkyl, aryl, heteroaryl, —NH_2, —NHR^{12}, and —$NR^{12}R^{13}$.

In one embodiment, in each of Formulas (I.a.10.j), (I.a.10.k) and (I.a.10.L):

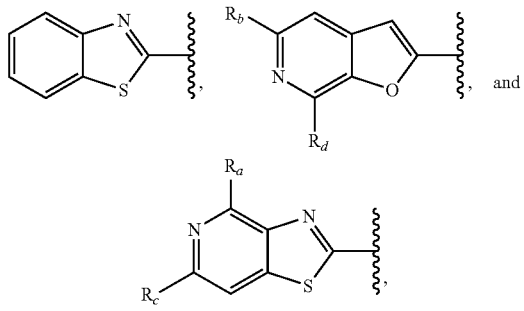
X and Y are each N;

Z is selected from the group consisting of H, —CH_3, and cyclopropyl;

R^2 is H;

R^1 is —NHR^{14} (wherein R^{14} is as defined in Formula (I)), and

R is selected from the group consisting of:



wherein:

R_a (when present) is selected from the group consisting of H, Me, Et, n-propyl, i-propyl, i-butyl, cyclopropyl, cyclobutyl, and amino;

R_b (when present) is selected from the group consisting of H, Me, Et, n-propyl, —OMe, and —OEt;

R_c (when present) is selected from the group consisting of H, Me, Et, and cyclopropyl; and

R_d (when present) is selected from the group consisting of H, Me, and Et.

In one embodiment, in each of Formulas (I.a.10.j), (I.a.10.k) and (I.a.10.L):

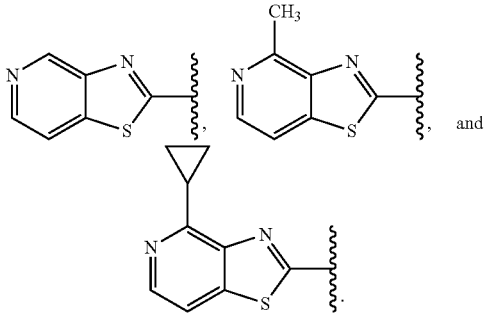
X and Y are each N;

Z is selected from the group consisting of H and —CH_3;

R^2 is H;

R^1 is —NHR^{14} (wherein R^{14} is as defined in Formula (I)); and

R is selected from the group consisting of:

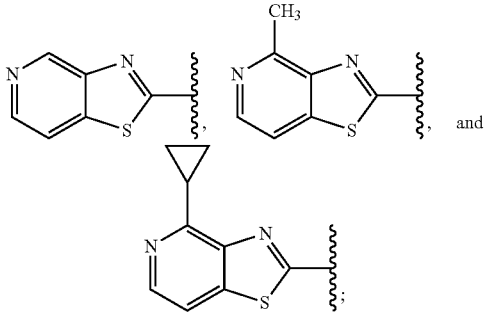


In another embodiment, in each of Formulas (I.a.10.j), (I.a.10.k) and (I.a.10.L),

X and Y are each N;

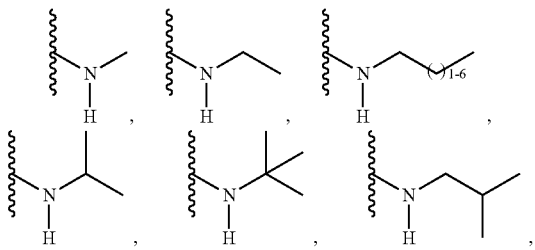
Z is selected from the group consisting of H and —CH_3;

R is selected from the group consisting of:



R^2 is H; and

R^1 is selected from the group consisting of:



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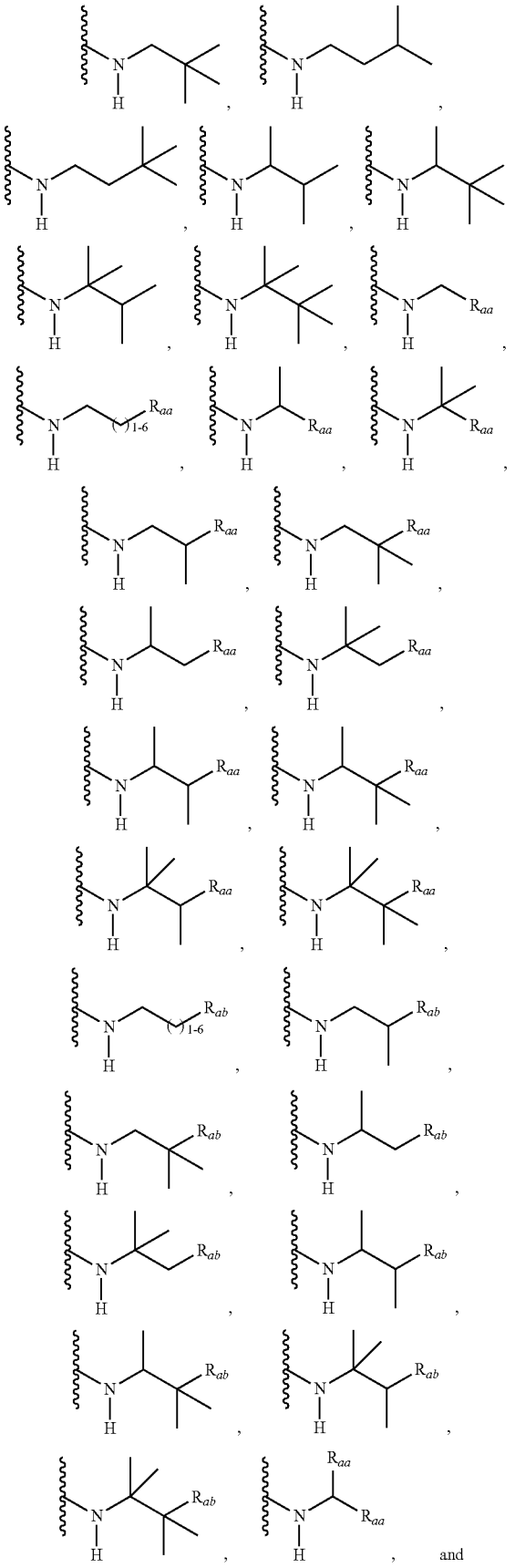

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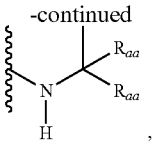


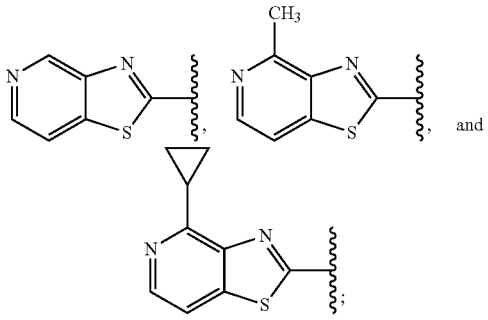
wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each R_{aa} is independently selected from haloalkyl (non-limiting examples of which include —CH_2F, —CHF_2, —CF_3, etc.), R_{ab} is selected from OH, OAc, and —O-alkyl (non-limiting examples of which include —O-Me, —O-Et, —O-n-Pr, —O-i-Pr, —O-n-Bu, —O-i-Bu, and —O-t-Bu), —O-haloalkyl (non-limiting examples of which include —O—CH_2F, —O—CHF_2, and —O—CF_3), —NH_2, —NHalkyl, and N(alkyl)$_2$.

In another embodiment, in each of Formulas (I.a.10.j), (I.a.10.k) and (I.a.10.L),

X and Y are each N;

Z is selected from the group consisting of H and —CH_3;

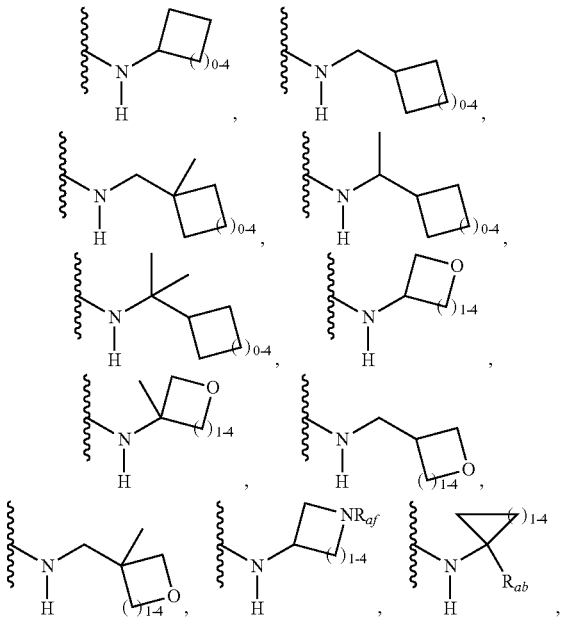
R is selected from the group consisting of:



and

R^2 is H; and

R^1 is selected from the group consisting of:



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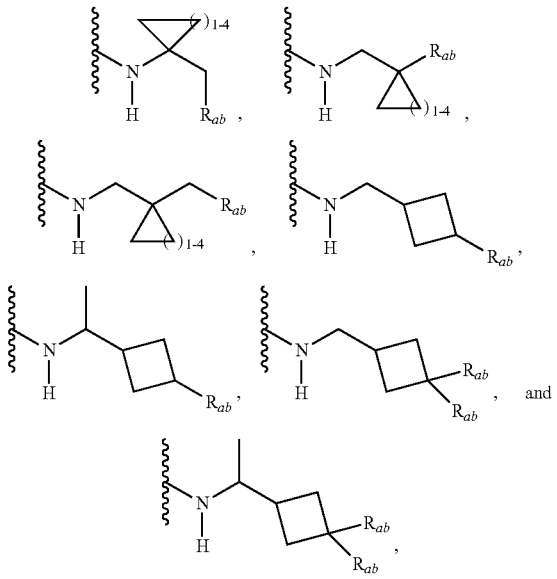


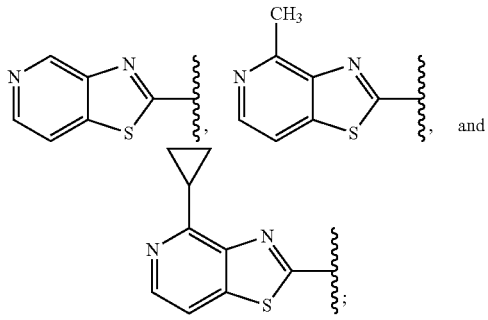
wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein R_{af} is selected from the group consisting of H and acetyl, and each R_{ab} is independently selected from the group consisting of OH, OAc, —Oalkyl, O-haloalkyl, halo, haloalkyl, alkyl, cycloalkyl, aryl, heteroaryl, —O-aryl, —S-aryl, —S-alkyl, —SO2-alkyl, —CO2-alkyl, —CO2H, and amino.

In another embodiment, in each of Formulas (I.a.10.j), (I.a.10.k) and (I.a.10.L),

X and Y are each N;

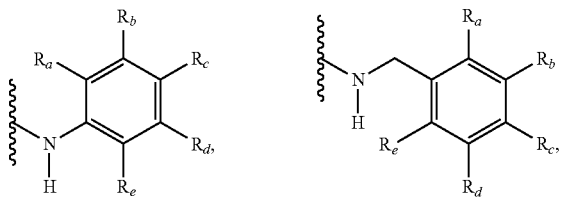
Z is selected from the group consisting of H and —CH_3;

R is selected from the group consisting of:



R^2 is H; and

R^1 is selected from the group consisting of:



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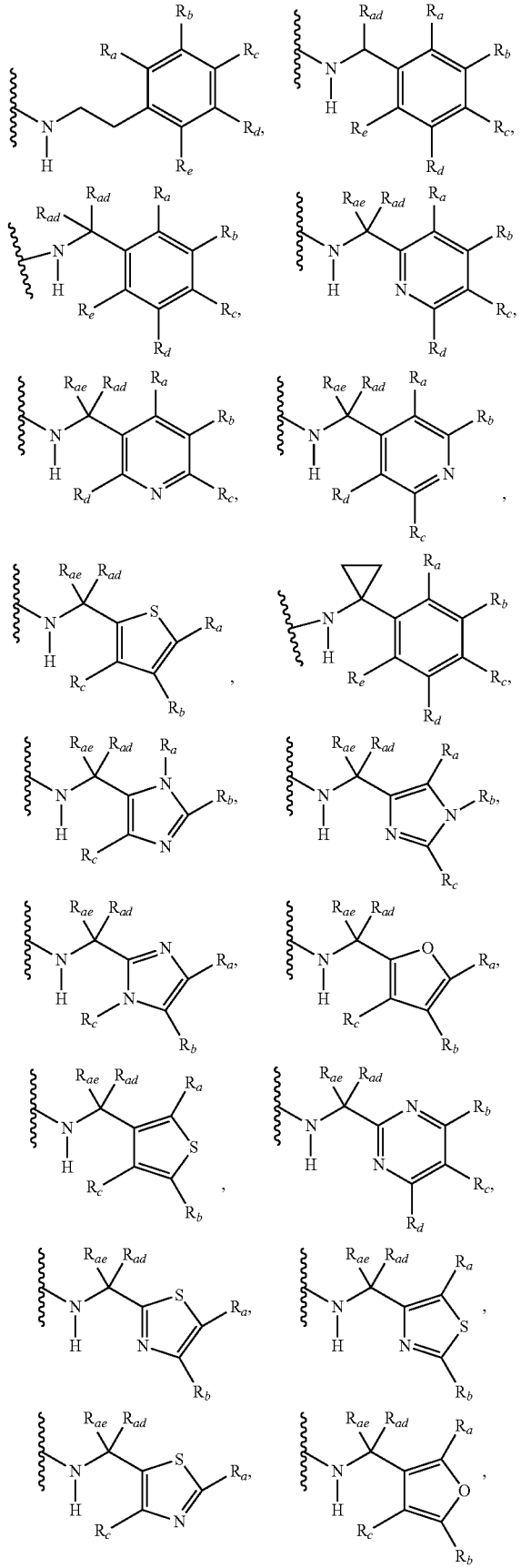

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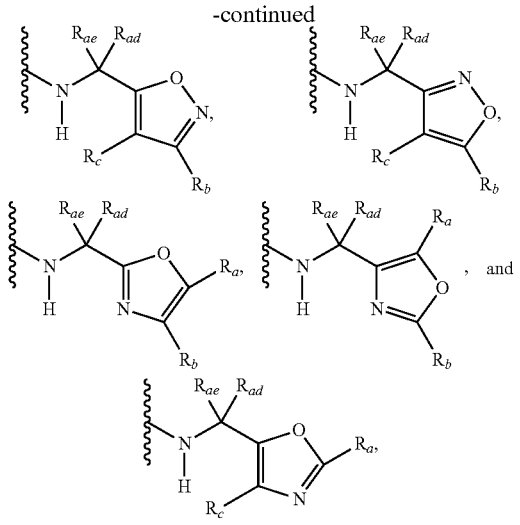


wherein the wavy line represents the point of attachment of R^1 to the rest of the molecule, and wherein each of R_a, R_b, R_c, R_d, and R_e, of R^1 is independently selected from H, halo, —OH, —CN, alkyl, haloalkyl, -alkyl-OH, heteroalkyl, heterohaloalkyl, —O-alkyl, —O-haloalkyl, —O-alkyl-OH, aryl, —O-aryl, —S-aryl, —O-alkyl-aryl, —S-alkyl-aryl, heteroaryl, —O-heteroaryl, —S-heteroaryl, —O-alkyl-heteroaryl, —S-alkyl-heteroaryl, heterocycloalkyl, —C(O)-alkyl, —C(O)-haloalkyl, —C(O)H, —C(O)OH, —C(O)O-alkyl, —OC(O)-alkyl, —C(O)NH_2, —C(O)NHR^{10}, —C(O)$NR^{10}R^{11}$, —C(O)ONH_2, —C(O)$ONHR^{10}$, —C(O)$ONR^{10}R^{11}$, —NH_2, —NHR^{10}, —$NR^{10}R^{11}$, —NO_2, substituted aryl, and substituted heteroaryl, wherein each of said substituted aryl and said substituted heteroaryl independently contains from one to three substituents, which may be the same or different, each substituent being independently selected from halo, alkyl, —O-alkyl, and —C(O)Oalkyl, and wherein each R_{ad} and each R_{ae} is independently selected from alkyl and haloalkyl.

In other embodiments, the compounds of the invention have a structural formula as depicted in the Tables below and include tautomers, and pharmaceutically acceptable salts, esters, prodrugs, isomers, and solvates of such compounds and such tautomers.

DEFINITIONS

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names and chemical structures may be used interchangeably to describe that same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portion of "hydroxyalkyl", "haloalkyl", arylalkyl-, alkylaryl-, "alkoxy" etc.

"At least one" means one or more than one, for example, 1, 2, or 3, or in another example, 1 or 2, or in another example 1.

"One or more" means one or more than one, for example, 1, 2, or 3, or in another example, 1 or 2, or in another example 1.

"Patient" includes both human and non-human animals. Non-human animals include research animals, farm animals, and companion animals such as mice, primates, monkeys, great apes, cows, sheep, horse, canine (e.g., dogs), and feline (e.g., house cats), etc.

"Composition" includes "pharmaceutical composition" and other compositions not suitable for pharmaceutical use but which may be suitable for other uses such as research or other uses.

"Pharmaceutical composition" (or "pharmaceutically acceptable composition") means a composition suitable for administration to a patient. Such compositions may contain the neat compound (or compounds) of the invention or mixtures thereof, or salts, solvates, prodrugs, isomers, or tautomers thereof, or they may contain one or more pharmaceutically acceptable carriers or diluents. The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being as described herein or independently selected from the group consisting of halo, alkyl, haloalkyl, spirocycloalkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, —NH(alkyl), —NH(cycloalkyl), —N(alkyl)$_2$, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, carboxy and —C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Aminoalkyl" means an alkyl which has been substituted at one or more available carbon atoms by one or more amino group(s). Non-limiting examples of such amino groups include those described herein, such as —NH_2, —NHR^{12}, —$NR^{12}R^{13}$, —NHR^{14}, and —NHR^{15}.

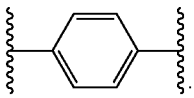
"Heteroalkyl" means an alkyl moiety as defined above, having one or more carbon atoms, for example one, two or three carbon atoms, including a terminal carbon atom, replaced with one or more heteroatoms, which may be the

same or different, where the point of attachment to the remainder of the molecule is through a carbon atom of the heteroalkyl radical. Suitable such heteroatoms include O, S, S(O), $S(O)_2$, —NH—, —N(alkyl)-, and $—N(alkyl)_2$. Non-limiting examples include ethers, thioethers, amines, hydroxymethyl, 3-hydroxypropyl, 1,2-dihydroxyethyl, 2-methoxyethyl, 2-aminoethyl, 2-dimethylaminoethyl, and the like. Additional non-limiting examples include -alkyl-NHalkyl and -alkyl-$N(alkyl)_2$. A non-limiting example of heteroalkyl wherein a terminal carbon atom is replaced with a heteroatom includes -alkyl-NH_2.

"Heterohaloalkyl" means an haloalkyl moiety as defined above, having one or more, for example one, two, or three carbon atoms, including a terminal carbon atom, replaced with one or more heteroatoms, which may be the same or different, where the point of attachment to the remainder of the molecule is through a carbon atom of the heterohaloalkyl radical.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and —S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene. More generally, the suffix "ene" on alkyl, aryl, heterocycloalkyl, etc. indicates a divalent moiety, e.g., $—CH_2CH_2—$ is ethylene, and



is para-phenylene.

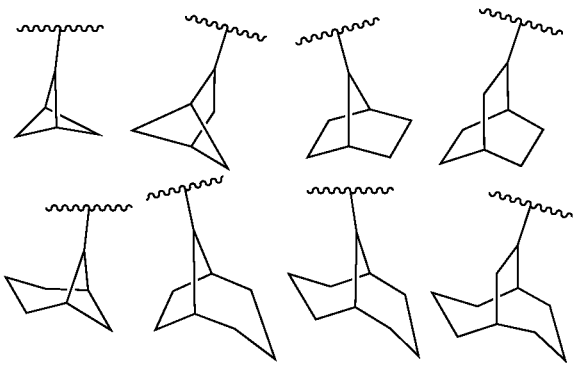
"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include —CH═CH—, $—C(CH_3)═CH—$, and $—CH═CHCH_2—$.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. Further non-limiting examples of cycloalkyl include the following:



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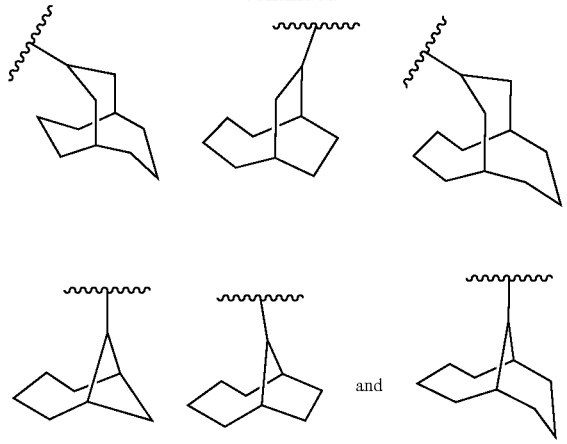
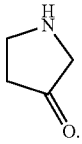


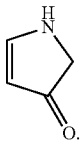
"Spirocycloalkyl" means a cycloalkyl moiety in which two available hydrogen atoms attached to the same carbon atom are replaced to form a cycloalkyl group.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

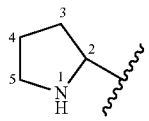
"Heterocycloalkyl" (or "heterocyclyl") means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any —NH in a heterocyclyl ring may exist protected such as, for example, as an —N(Boc), —N(CBz), —N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Thus, the term "oxide," when it appears in a definition of a variable in a general structure described herein, refers to the corresponding N-oxide, S-oxide, or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Such =O groups may be referred to herein as "oxo." An example of such a moiety is pyrrolidinone (or pyrrolidone):



"Heterocycloalkenyl" (or "heterocyclenyl") means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" also includes rings wherein =O replaces two available hydrogens on the same carbon atom (i.e., heterocyclyl includes rings having a carbonyl group in the ring). Example of such moiety is pyrrolidenone (or pyrrolone):



It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



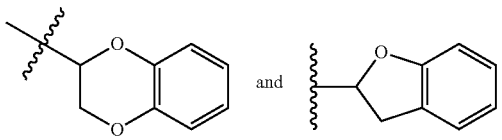
there is no —OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms of the compounds of the invention are also contemplated as being within the scope of the invention.

"Arylcycloalkyl" (or "arylfused cycloalkyl") means a group derived from a fused aryl and cycloalkyl as defined

herein. Preferred arylcycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and cycloalkyl consists of about 5 to about 6 ring atoms. The arylcycloalkyl can be optionally substituted as described herein. Non-limiting examples of suitable arylcycloalkyls include indanyl (a benzofused cycloalkyl) and 1,2,3,4-tetrahydronaphthyl and the like. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylheterocycloalkyl" (or "arylfused heterocycloalkyl") means a group derived from a fused aryl and heterocycloalkyl as defined herein. Preferred arylheterocycloalkyls are those wherein aryl is phenyl (which may be referred to as "benzofused") and heterocycloalkyl consists of about 5 to about 6 ring atoms. The arylheterocycloalkyl can be optionally substituted, and/or contain the oxide or oxo, as described herein. Non-limiting examples of suitable arylfused heterocycloalkyls include:



The bond to the parent moiety is through a non-aromatic carbon atom.

It is also understood that the terms "arylfused aryl", "arylfused cycloalkyl", "arylfused cycloalkenyl", "arylfused heterocycloalkyl", arylfused heterocycloalkenyl", "arylfused heteroaryl", "cycloalkylfused aryl", "cycloalkylfused cycloalkyl", "cycloalkylfused cycloalkenyl", "cycloalkylfused heterocycloalkyl", "cycloalkylfused heterocycloalkenyl", "cycloalkylfused heteroaryl, "cycloalkenylfused aryl", "cycloalkenylfused cycloalkyl", "cycloalkenylfused cycloalkenyl", "cycloalkenylfused heterocycloalkyl", "cycloalkenylfused heterocycloalkenyl", "cycloalkenylfused heteroaryl", "heterocycloalkylfused aryl", "heterocycloalkylfused cycloalkyl", "heterocycloalkylfused cycloalkenyl", "heterocycloalkylfused heterocycloalkyl", "heterocycloalkylfused heterocycloalkenyl", "heterocycloalkylfused heteroaryl", "heterocycloalkenylfused aryl", "heterocycloalkenylfused cycloalkyl", "heterocycloalkenylfused cycloalkenyl", "heterocycloalkenylfused heterocycloalkyl", "heterocycloalkenylfused heterocycloalkenyl", "heterocycloalkenylfused heteroaryl", "heteroarylfused aryl", "heteroarylfused cycloalkyl", "heteroarylfused cycloalkenyl", "heteroarylfused heterocycloalkyl", "heteroarylfused heterocycloalkenyl", and "heteroarylfused heteroaryl" are similarly represented by the combination of the groups aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, and heteroaryl, as previously described. Any such groups may be unsubstituted or substituted with one or more ring system substituents at any available position as described herein.

"Aralkyl" or "arylalkyl" means an aryl-alkyl-group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl. The term (and similar terms) may be written as "arylalkyl-" to indicate the point of attachment to the parent moiety.

Similarly, "heteroarylalkyl", "cycloalkylalkyl", "cycloalkenylalkyl", "heterocycloalkylalkyl", "heterocycloalkenylalkyl", etc., mean a heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, etc. as described herein bound to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

Similarly, "arylfused arylalkyl-", arylfused cycloalkylalkyl-, etc., means an arylfused aryl group, arylfused cycloalkyl group, etc. linked to a parent moiety through an alkyl group. Preferred groups contain a lower alkyl group. Such alkyl groups may be straight or branched, unsubstituted and/or substituted as described herein.

"Alkylaryl" means an alkyl-aryl-group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkylether" means a non-aromatic ring of 3 to 7 members comprising an oxygen atom and 2 to 7 carbon atoms. Ring carbon atoms can be substituted, provided that substituents adjacent to the ring oxygen do not include halo or substituents joined to the ring through an oxygen, nitrogen or sulfur atom.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl, adamantylpropyl, and the like.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclylalkyl" (or "heterocycloalkylalkyl") means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

"Alkynylalkyl" means an alkynyl-alkyl-group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl-group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl-group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Cyanoalkyl" means a NC-alkyl-group in which alkyl is as previously defined. Preferred cyanoalkyls contain lower alkyl. Non-limiting examples of suitable cyanoalkyl groups include cyanomethyl and 2-cyanoethyl.

"Acyl" means an H—C(O)—, alkyl-C(O)— or cycloalkyl-C(O)—, group in which the various groups are as previously described. The bond to the parent moiety is

through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)— group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1-naphthoyl.

"Heteroaroyl" means an heteroaryl-C(O)— group in which the heteroaryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include pyridoyl.

"Alkoxy" means an alkyl-O— group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkyoxyalkyl" means a group derived from an alkoxy and alkyl as defined herein. The bond to the parent moiety is through the alkyl.

"Aryloxy" means an aryl-O— group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" (or "arylalkyloxy") means an aralkyl-O— group (an arylaklyl-O— group) in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Arylalkenyl" means a group derived from an aryl and alkenyl as defined herein. Preferred arylalkenyls are those wherein aryl is phenyl and the alkenyl consists of about 3 to about 6 atoms. The arylalkenyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Arylalkynyl" means a group derived from a aryl and alkenyl as defined herein. Preferred arylalkynyls are those wherein aryl is phenyl and the alkynyl consists of about 3 to about 6 atoms. The arylalkynyl can be optionally substituted by one or more substituents. The bond to the parent moiety is through a non-aromatic carbon atom.

"Alkylthio" means an alkyl-S— group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S— group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S— group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O—CO— group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O—C(O)— group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O—C(O)— group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$— group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$— group. The bond to the parent moiety is through the sulfonyl.

"Spirocycloalkyl" means a cycloalkyl group attached to a parent moiety at a single carbon atom. Non-limiting examples of spirocycloalkyl wherein the parent moiety is a cycloalkyl include spiro[2.5]octane, spiro[2.4]heptane, etc. Non-limiting examples of spirocycloalkyl wherein the parent moiety is an The alkyl moiety linking fused ring systems (such as the alkyl moiety in heteroarylfused heteroarylalkyl-) may optionally be substituted with spirocycloalkyl or other groups as described herein. Non-limiting spirocycloalkyl groups include spirocyclopropyl, spriorcyclobutyl, spirocycloheptyl, and spirocyclohexyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

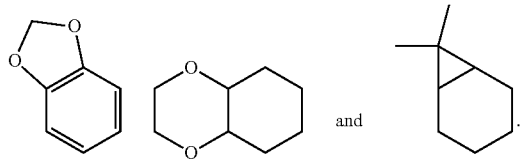
Substitution on a cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylfused cycloalkylalkyl-moiety or the like includes substitution on any ring portion and/or on the alkyl portion of the group.

When a variable appears more than once in a group, e.g., R^8 in $—N(R^8)_2$, or a variable appears more than once in a structure presented herein such as Formula (I), the variables can be the same or different.

With reference to the number of moieties (e.g., substituents, groups or rings) in a compound, unless otherwise defined, the phrases "one or more" and "at least one" mean that there can be as many moieties as chemically permitted, and the determination of the maximum number of such moieties is well within the knowledge of those skilled in the art. With respect to the compositions and methods comprising the use of "at least one compound of the invention, e.g., of Formula (I)," one to three compounds of the invention, e.g., of Formula (I) can be administered at the same time, preferably one.

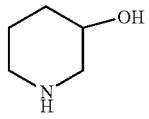
Compounds of the invention may contain one or more rings having one or more ring system substituents. "Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being as described herein or independently selected from the group consisting of alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, —O—C(O)-alkyl, —O—C(O)-aryl, —O—C(O)-cycloalkyl, —C(=N—CN)—NH_2, —C(=NH)—NH_2, —C(=NH)—NH(alkyl), Y_1Y_2N—, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$—, $Y_1Y_2NSO_2$—

and —$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moieties are rings such as heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, and heterocycloalkenyl rings. Additional non-limiting examples include methylene dioxy, ethylenedioxy, —$C(CH_3)_2$— and the like which form moieties such as, for example:

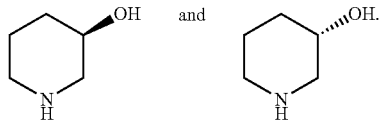


As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

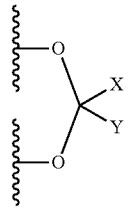
The line ----, as a bond generally indicates a mixture of, or either of, the possible isomers, e.g., containing (R)- and (S)-stereochemistry. For example:



means containing both

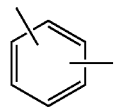


The wavy line , as used herein, indicates a point of attachment to the rest of the compound. For example, each wavy line in the following structure:



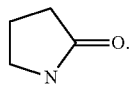
indicates a point of attachment to the core structure, as described herein.

Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring carbon atoms.

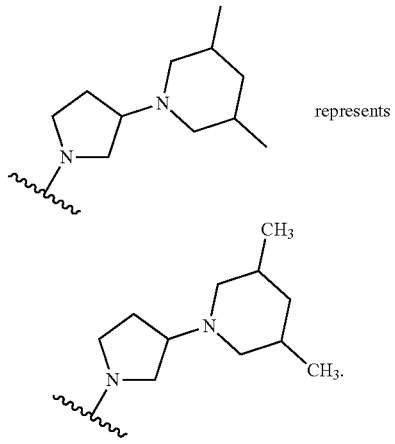
"Oxo" is defined as a oxygen atom that is double bonded to a ring carbon in a cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, or other ring described herein, e.g.,



In this specification, where there are multiple oxygen and/or sulfur atoms in a ring system, there cannot be any adjacent oxygen and/or sulfur present in said ring system.

It is noted that the carbon atoms for compounds of the invention may be replaced with 1 to 3 silicon atoms so long as all valency requirements are satisfied.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon (or other atom or heteroatom) with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when

the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene et al, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g., a drug precursor) that is transformed in vivo to yield a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, $(C_1$-$C_8)$alkyl, $(C_2$-$C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino) ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N—$(C_1$-$C_2)$alkylamino$(C_2$-$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$-$C_2)$alkyl, N,N-di$(C_1$-$C_2)$alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$-$C_3)$alkyl, and the like.

Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, $(C_1$-$C_6)$alkanoyloxymethyl, 1-$((C_1$-$C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1$-$C_6)$alkanoyloxy)ethyl, $(C_1$-$C_6)$alkoxycarbonyloxymethyl, N—$(C_1$-$C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1$-$C_6)$alkanoyl, α-amino$(C_1$-$C_4)$alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, —$P(O)(O(C_1$-$C_6)$alkyl$)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of the invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently $(C_1$-$C_{10})$alkyl, $(C_3$-$C_7)$cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, $(C_1$-$C_6)$alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is $(C_1$-$C_4)$alkyl and Y^3 is $(C_1$-$C_6)$alkyl, carboxy $(C_1$-$C_6)$alkyl, amino$(C_1$-$C_4)$alkyl or mono-N- or di-N,N—$(C_1$-$C_6)$alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N—$(C_1$-$C_6)$alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira et al, *J. Pharmaceutical Sci.,* 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder et al, *AAPS PharmSciTech.,* 5(1), article 12 (2004); and A. L. Bingham et al, *Chem. Commun.,* 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of the invention can form salts which are also within the scope of this invention. Reference to a compound of the invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of the invention contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the invention may be formed, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates,

maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge et al, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson et al, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di(C_{6-24}) acyl glycerol.

Compounds of the invention, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of the invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of the invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of the invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a compound of the invention incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention).

Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of the invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of the

invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of the invention, and of the salts, solvates, esters and prodrugs of the compounds of the invention, are intended to be included in the present invention.

Suitable doses for administering compounds of the invention to patients may readily be determined by those skilled in the art, e.g., by an attending physician, pharmacist, or other skilled worker, and may vary according to patient health, age, weight, frequency of administration, use with other active ingredients, and/or indication for which the compounds are administered. Doses may range from about 0.001 to 500 mg/kg of body weight/day of the compound of the invention. In one embodiment, the dosage is from about 0.01 to about 25 mg/kg of body weight/day of a compound of the invention, or a pharmaceutically acceptable salt or solvate of said compound. In another embodiment, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application. In another embodiment, a typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

As discussed above, the amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated.

When used in combination with one or more additional therapeutic agents, the compounds of this invention may be administered together or sequentially. When administered sequentially, compounds of the invention may be administered before or after the one or more additional therapeutic agents, as determined by those skilled in the art or patient preference.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an effective amount of one or more additional agents described above.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. Certain assays are exemplified elsewhere in this document.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pa.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

In one embodiment, the compound is administered orally.

In some embodiments, it may be advantageous for the pharmaceutical preparation comprising one or more compounds of the invention be prepared in a unit dosage form. In such forms, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

PREPARATIVE EXAMPLES

Compounds of the invention can be made using procedures known in the art. The following reaction schemes show typical procedures, but those skilled in the art will recognize that other procedures can also be suitable.

Techniques, solvents and reagents may be referred to by their following abbreviations:

Thin layer chromatography: TLC
High performance liquid chromatography: HPLC
ethyl acetate: AcOEt or EtOAc
methanol: MeOH
ether: Et_2O
tetrahydrofuran: THF
Acetonitrile: MeCN
1,2-dimethoxyethane: DME
Trifluoroacetic acid: TFA
Dimethylacetamide: DMA
Dimethylformamide: DMF
Dimethylsulfoxide: DMSO
triethylamine: Et_3N or TEA
tert-Butoxycarbonyl: t-Boc or Boc
2-(Trimethylsilyl)ethoxycarbonyl: Teoc
nuclear magnetic resonance spectroscopy: NMR
liquid chromatography mass spectrometry: LCMS
high resolution mass spectrometry: HRMS
milliliters: mL
millimoles: mmol
microliters: μl
grams: g
milligrams: mg
centimeters: cm
room temperature (ambient, about 25° C.): rt

Retention time: tR

N-bromosuccinimide: NBS

N-chlorosuccinimide: NCS

Methyl magnesium bromide: MeMgBr

iron(III) acetylacetonate: $Fe(acac)_3$

Diphenylphosphoryl azide: DPPA

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride: EDCl

Diisopropylethylamine: DIEA or i-Pr_2NEt or DIPEA

Diisopropylamine: i-Pr_2NH

2-(Trimethylsilyl)ethanol: TMSethanol

3-Chloroperoxybenzoic acid: mCPBA

n-Butyllithium: nBuLi

lithium diisopropylamide: LDA

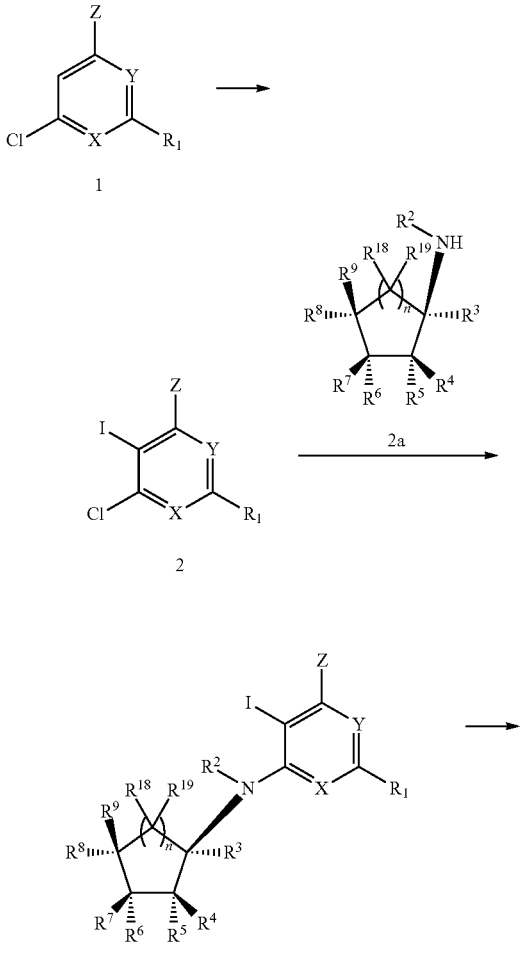
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II): $PdCl_2dppf$

Palladium(II)acetate: $Pd(OAc)_2$

Methanesulfonyl chloride: $MeSO_2Cl$

Triphenyl phosphine: TPP or Ph_3P

General Method I:



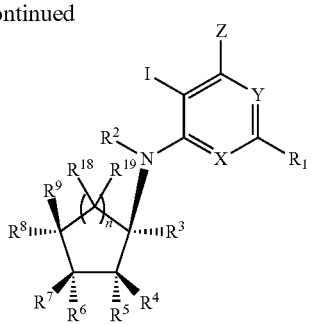
1

2a

2

3

-continued



4

wherein X, Y, Z, R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19}, and n are all variables as defined herein.

Example 5

Procedure A-1

To a stirred mixture of 2-amino-4,6-dichloropyrimidine (1, X, Y=N, Z=Cl, 5.0 g, 30.5 mmol) in glacial acetic acid (120 mL) was added dropwise a solution of ICl (5.01 mL, 100 mmol) in glacial acetic acid (120 mL). After 5 h, the mixture was filtered, and the collected solids were washed with glacial acetic acid and then azeotroped with toluene (2×), giving 2.78 g of 2 as a white solid. After 7 days, more solid was visible in the filtrate, and thus, it was again filtered, the collected solids washed with glacial acetic acid and azeotroped with toluene (2×), giving another 4.22 g of 2, with TLC and MS data that matched the first batch.

MS m/z $(M+H)^+$ 289.93 (2 Cl pattern);

A mixture of 2 (58.0 g, 0.20 mol), the cyclopentylamine sugar (1R,2S,3R,4R)-2,3-dihydroxy-4-(hydroxymethyl)-1-aminocyclopentane hydrochloride 2a, (40.4 g, 0.22 mol) in ethanol (800 ml) and triethylamine (92 ml, 0.66 mol) was refluxed for 18 h, during which time complete dissolution occurred. After concentrating and adsorbing the residue onto silica gel, the crude was purified by chromatography, eluting with a gradient of EtOAc/MeOH (97.5/2.5→95/5). The desired product 3 (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH) was obtained as a white solid (67 g).

MS m/z $(M+H)^+$ 401.00 (Cl pattern);

^1H NMR (300 MHz, DMSO-d6) δ 6.61 (s, 2H, 2H D_2O exchangeable), 6.22 (d, 1H, J=7.7 Hz, D_2O exchangeable), 4.75 (dd, 1H, J=4.8, 4.8 Hz, D_2O exchangeable), 4.60 (d, 1H, J=5.2 Hz, D_2O exchangeable), 4.41 (d, 1H, J=4.5 Hz, D_2O exchangeable), 4.30-4.18 (m, 1H; upon D_2O exchange collapses to 4.22, dd, J=7.4, 12.9 Hz), 3.77-3.70 (m, 2H), 3.39 (dd, 2H, J=5.1, 5.1 Hz; upon D_2O exchange collapses to 3.43, d, J=5.3 Hz), 2.24-2.14 (m, 1H), 1.93-1.83 (m, 1H), 1.15-1.06 (m, 1H).

Analysis calculated for $C_{16}H_{18}Cl_2N_6O_3$: C, 46.50; H, 4.39; N, 20.34. Found: C, 46.25; H, 4.26; N, 20.09.

Example 5

(1R,2S,3R,5R)-3[(2-amino-6-chloro-5-phenyl-4-pyrimidinyl)amino]-5-hydroxymethyl)-1,2-cyclopentanol

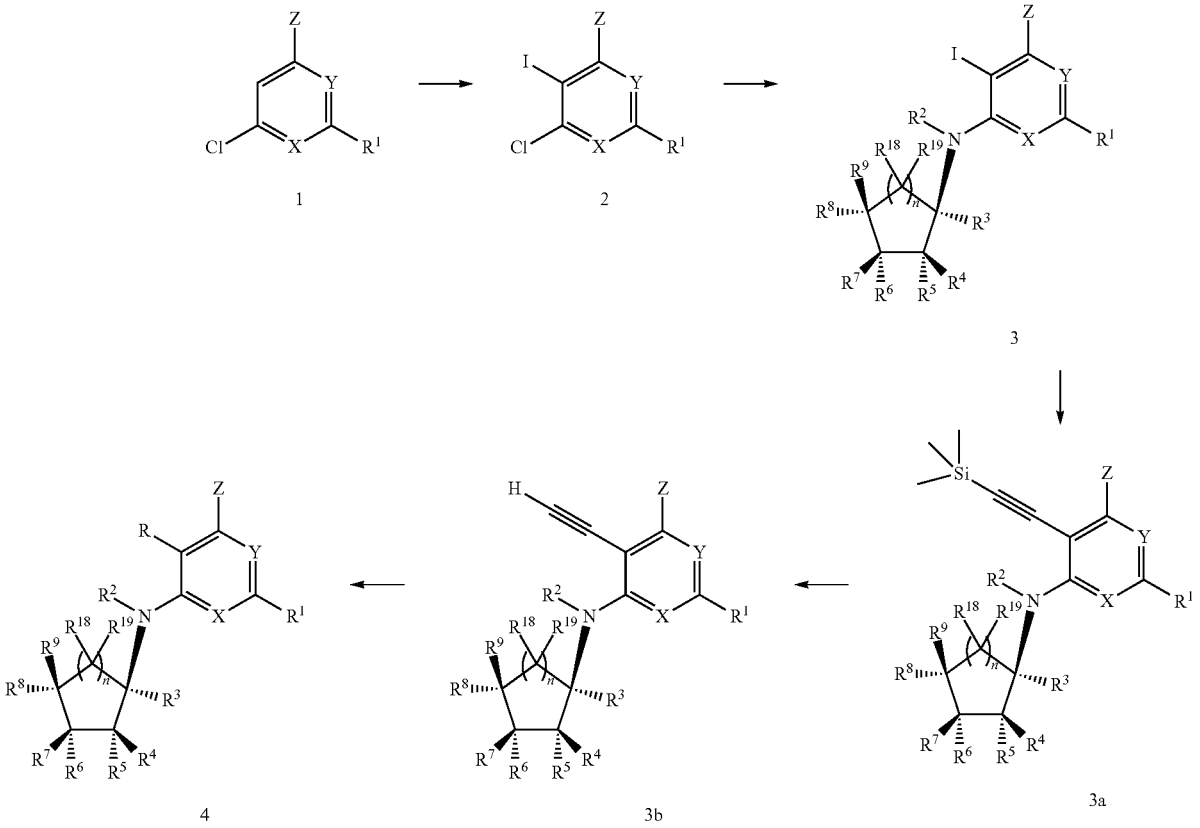
To a stirring solution of compound 3 (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH,

0.1 g; 0.25 mmol) (under Ar at room temperature) and phenylboronic acid (0.04 g; 0.3 mmol) in anhydrous DMF (5.0 mL) was added anhydrous K_2CO_3 (0.17 g; 1.25 mmol). After 5.0 min, tetrakis(triphenylphosphine)-palladium (0) (0.014 g; 0.012 mmol) was added. The reaction vessel (RB flask) was then covered with aluminum foil and stiffed at 90° C. for 24 h. Then, the reaction mixture was cooled to room temperature (22° C.), and the solvent was removed in vacuo and then co-evaporated with MeOH. The obtained brown residue was purified by column chromatography, eluting with 94:6 $CHCl_3$/MeOH (V/V) (Fisher), giving the pure product 5 (Structure 4, General Method I, R=phenyl, X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH) as an off-white solid (0.045 g).

the reaction mixture was heated in an oil bath at 55° C. for 18 h. After concentrating, the methanol extract was filtered, and the filtrate concentrated onto silica. Chromatography on silica (eluting gradient of $CHCl_3$/MeOH (95/5→90/10) gave 2.62 g of a brown foam that contained triethylamine salts. A second chromatography (eluting with EtOAc/MeOH, 95/5) gave 2.55 g of 3a (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH) as a reddish brown solid. (Even after the 2 chromatographic isolations, the obtained 3a still contained impurities, by TLC, that was used as is in the next reaction.)

^{1}H NMR (300 MHz, DMSO-d6) δ 6.94 (s, 2H), 6.10 (d, 1H, J=7.7 Hz), 4.68-4.62 (m, 2H), 4.45 (d, 1H, J=4.5 Hz),

General Method II:



Wherein X, Y, Z, R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{18}, R^{19} and n are all variables as defined herein.

Example 9

Procedure A-2

To a degassed solution of 3 (synthesis previously described, X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH, 5.0 g, 12.5 mmol) in DMF (50 ml) was added (with protection from light) triethylamine (7.0 mL, 50 mmol) dropwise over 10 min, followed by CuI (952 mg, 5.0 mmol) and then tetrakis(triphenylphosphine)palladium (2.9 g, 2.5 mmol). After degassing with Ar for 10 min, the addition of TMS acetylene (5.3 mL, 37.5 mmol) was followed by sealing the reaction vessel with a rubber septum. Then, while still protecting the sealed flask from light,

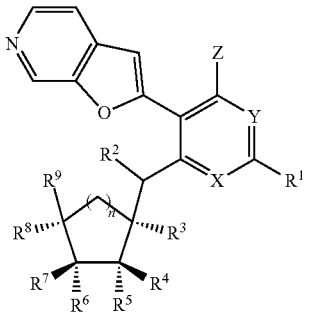
4.27-4.17 (m, 1H), 3.76-3.65 (m, 2H), 3.40 (dd, 2H, J=5.1, 5.1 Hz), 2.26-2.16 (m, 1H), 1.93-1.83 (m, 1H), 1.16-1.07 (m, 1H), 0.23 (s, 3H).

To a solution of 3a (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH) 4.17 g, 11.2 mmol) in acetonitrile (100 ml) was added tetraethylammonium fluoride dihydrate (1.04 g, 5.62 mmol). After 2 h, MeOH was added to dissolve precipitated material, and the resulting solution was concentrated onto silica gel. Chromatography on silica (eluting gradient of $CHCl_3$/MeOH, 95/5→92.5/7.5) followed by chromatography eluting with EtOAc/MeOH (95/5) resulted in the recovery of 3.06 g of 3b (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH) as a light tan solid.

^{1}H NMR (DMSOd_6): δ 1.10 (m, 1H), 1.89 (m, 1H), 2.15 (m, 1H), 3.38 (t, J=5.1 Hz, 2H), 3.73 (m, 2H), 4.28 (m, 1H), 4.40 (d, 1H, J=3.9 Hz), 4.58 (d, 1H, J=5.1 Hz), 4.71 (t, 1H, J=5.1 Hz), 6.58 (d, 1H, J=8.1 Hz), 6.87 (s, 2H)

MS m/z $(M+H)^+$: 299.15 (Cl pattern);

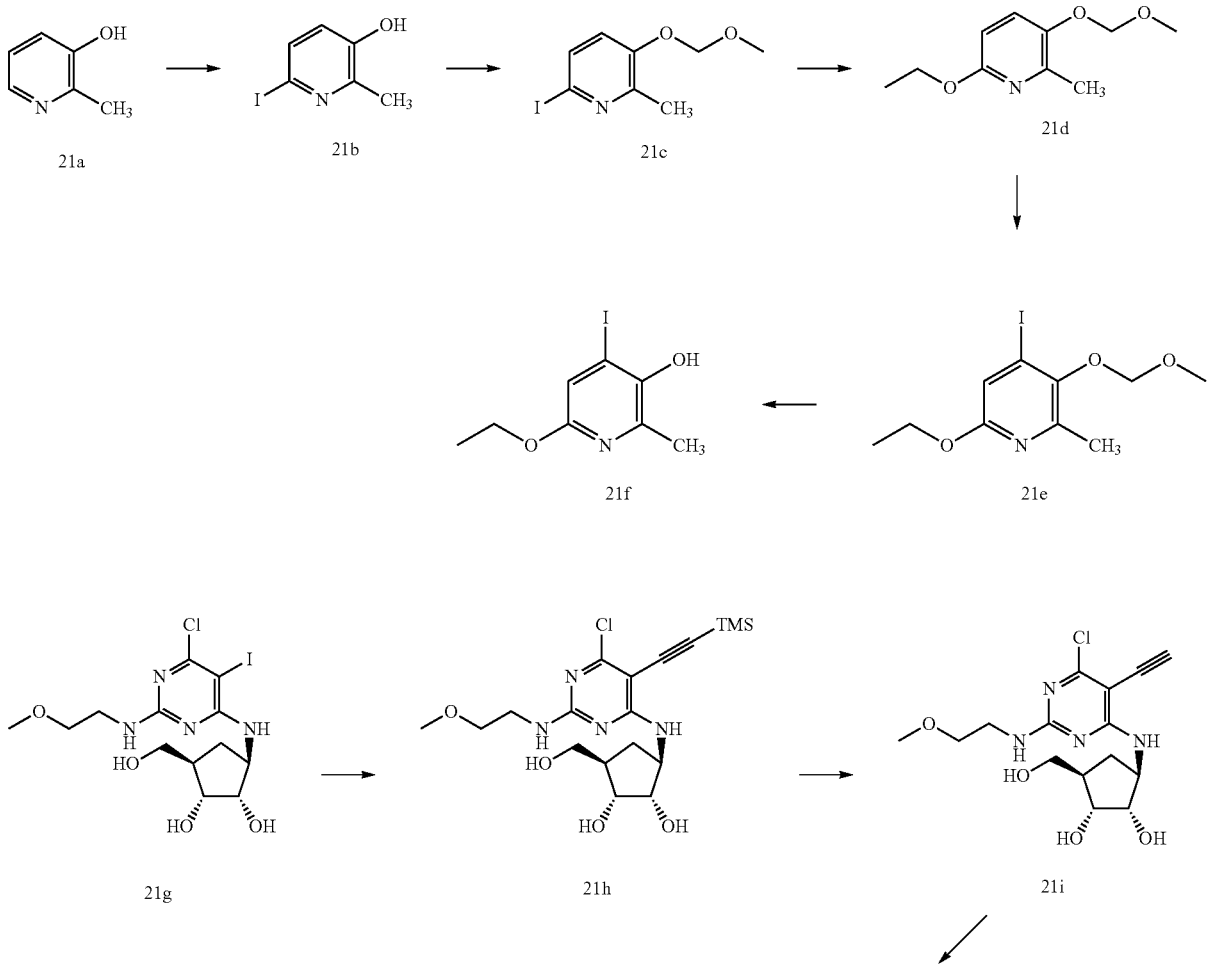
Example 9



To a degassed solution of 3b (150 mg, 0.50 mmol) and a 1-halo, 2-hydroxy or thio-aryl compound (e.g., 4-iodo-3-pyridinol, 261 mg, 1.5 mmol) in DMF (5 ml) was added (with protection from light) triethylamine (0.28 ml, 2.0 mmol), followed by CuI (38 mg, 0.2 mmol) and then tetrakis(triphenylphosphine)palladium (116 mg, 0.1 mmol). After sealing the reaction vessel with a rubber septum, the reaction mixture was heated in an oil bath at 40° C. for 18 h. After concentrating, the methanol extract was filtered and the filtrate chromatographed, using an elution gradient of $CHCl_3$/MeOH (95/5→90/10). Example 9 (X, Y=N, Z=Cl, R^1=NH_2, R^2, R^3, R^4, R^7, R^8=H, R^5, R^6=OH, R^9=CH_2OH, 24 mg) was recovered as yellow crystals after recrystallizing from MeOH.

Analysis calculated for $C_{17}H_{18}ClN_5O_4$.0.1 MeOH.1.1 SiO_2: C, 44.70; H, 4.04; N, 15.24. Found: C, 44.72; H, 4.20; N, 15.24.

Example 21



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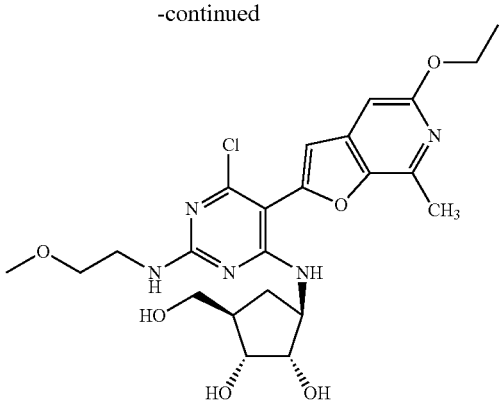


21

To a stirred solution of potassium carbonate (111 g, 0.80 mol) in water (350 ml) at room temperature under Ar was added 3-hydroxy-2-methylpyridine (21a, 25.6 g, 0.23 mol). After cooling in an ice bath, iodine (70.0 g, 0.28 mol) was added, and the reaction was allowed to warm to room temperature overnight. After adding saturated aqueous sodium thiosulfate, the reaction mixture was acidified with conc. aqueous HCl to a pH of 2, followed by extraction with ethyl acetate (3×). The combined organic extract was washed with water, saturated brine, dried with sodium sulfate, and then concentrated. Recovered 55.5 g of crude product that was chromatographed on silica, eluting with a EtOAc/hexanes gradient (0/100→75/25). Recovered 21b (33.7 g) as a slightly yellow solid.

To a stirred mixture of 21b (33.7 g, 0.143 mol) in methylene chloride (400 ml) under Ar and cooled in a dry ice/acetone bath was added chloromethyl methyl ether (12.5 ml, 0.165 mol). After 15 min, diisopropylethyl amine (37.4 ml, 0.215 mol) was added dropwise over 30 min. The resulting mixture was then allowed to slowly warm to room temperature overnight. The reaction solution was washed with water (2×), saturated brine, dried with sodium sulfate, and concentrated. Recovered 37.4 g of crude product that was chromatographed on silica, eluting with a EtOAc/hexanes gradient (0/100→90/10). Recovered 21c (36.0 g) as a slightly colored oil.

To a solution of 21c (2.5 g, 8.96 mmol) in absolute ethanol (25 ml) was added sodium ethoxide (3.8 g, 44.8 mmol) followed by sonication to give an orange solution. After adding copper (I) bromide (262 mg, 1.79 mmol), the resulting mixture was placed in a preheated oil bath at 95° C. After 4.5 h, the reaction was cooled to room temperature and then filtered through a short pad of celite, washing with ethanol. Combined filtrate was concentrated, followed by partitioning with ethyl acetate and water. The separated aqueous layer was further extracted with ethyl acetate. The combined organic extract was washed saturated brine, dried ($MgSO_4$), and concentrated. Recovered 1.72 g of crude product that was chromatographed on silica, eluting with a EtOAc/hexanes gradient (0/100→90/10). Recovered 21d (1.60 g) as a slightly yellow oil.

To a solution of 21d (1.20 g, 6.1 mmol) in THF under Ar, a solution of 1.6M nBuLi in hexanes (4.2 ml, 6.7 mmol) was added dropwise at a rate to keep the reaction temperature < −70° C. After 1 h, a solution of iodine (1.85 g, 7.3 mmol) in THF (25 ml) was added dropwise again at a rate to keep the reaction temperature <−70° C. After 2 h, dilute aqueous ammonium chloride was added, and the reaction was allowed to warm to room temperature. After partitioning between ethyl acetate and water, the organic extract was washed saturated aqueous sodium thiosulfate, water, saturated brine, dried with sodium sulfate, and concentrated. Recovered 2.07 g of crude product that was then chromatographed on silica eluting with EtOAc/hexanes (25/75). Recovered 21e (1.77 g) as a slightly yellow oil that contained (by NMR) 10% starting material.

To a solution of 21e (1.77 g, 5.48 mmol) in methylene chloride (50 ml) under Ar cooled in an ice/water bath was added trifluoroacetic acid (10.2 ml, 137 mmol). After allowing to warm room temperature while stiffing overnight, the solution was diluted with methylene chloride and carefully washed saturated aqueous sodium bicarbonate until the aqueous layer was basic. The organic extract was washed water, saturated brine, dried with sodium sulfate, and concentrated, giving 21f (1.16 g) of 2,4,6-trichloropyrimidine as a yellow solid that was used as is.

Compound 21g was prepared from 2,4,6-trichloropyrimidine in a fashion similar to 124e.

To a degassed solution of 21g (2.64 g, 5.75 mmol) in dioxane (50 ml) was added triethylamine (3.2 ml, 23 mmol) followed by CuI (219 mg, 1.15 mmol) and then dichlorobis (triphenylphosphine) palladium (404 mg, 0.575 mmol). After degassing with Ar for 10 min, the addition of TMS acetylene (2.44 ml, 17.3 mmol) was followed by sealing of the reaction vessel with a rubber septum. While protecting from light, the sealed flask was heated in an oil bath at 50° C. for 20 h. After concentrating onto silica, the residue was chromatographed on silica, eluting with a $CHCl_3$/MeOH gradient (100/0→90/10). Recovered a product that contained triethylamine salts. After chromatography on silica eluting with EtOAc/MeOH (100/0→90/10), recovered 1.71 g of 21h as a purple foam.

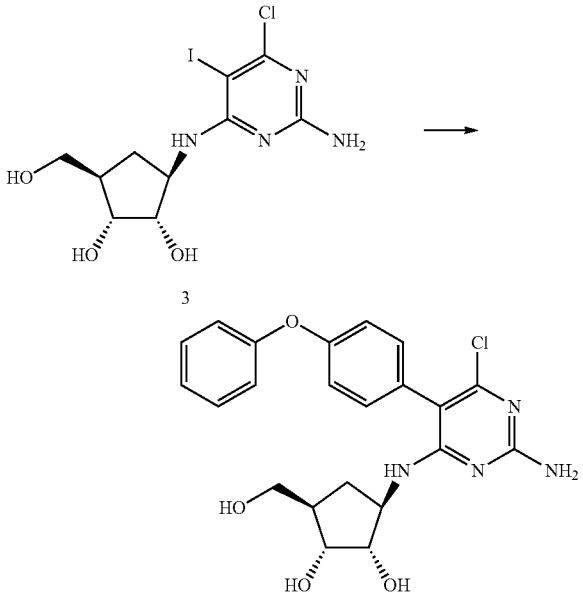
To a solution of 21h (1.7 g, 3.96 mmol) in acetonitrile (25 ml) was added tetraethylammonium fluoride dihydrate (367 mg, 1.98 mmol). After stiffing overnight, the reaction mixture was concentrated onto silica gel and chromatographed on silica, eluting with a $CHCl_3$/MeOH gradient (100/0→95/5). Recovered 1.32 g of 21i as a light brown crystalline solid.

To a degassed solution of 21i (178 mg, 0.50 mmol) and 21f (167 mg, 0.60 mmol) in DMF (5 ml) was added triethylamine (0.35 ml, 2.5 mmol) followed by CuI (19 mg, 0.1 mmol) and then tetrakistriphenylphosphine palladium

(58 mg, 0.05 mmol). After sealing, the reaction vial was microwaved (300 W) at 90° C. for 10 min. After concentrating, the methanol extract was concentrated onto silica and chromatographed eluting with a $CHCl_3$/MeOH gradient (100/0→90/10). Recovered 236 mg of a yellow solid that was purified by reverse phase HPLC (Phenomenex Luna C-18 column) using water/MeCN (containing 0.1% TFA) gradient. Recovered 104 mg of 21 as a yellow solid.

Example 101

Procedure A



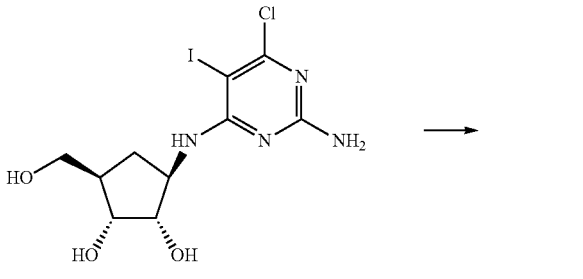
3

101

A mixture of 3 (previously described, 40 mg, 0.1 mmol), 4-phenoxyphenyl boronic acid (63 mg, 0.3 mmol), potassium carbonate (69 mg, 0.5 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (II) (16 mg, 0.02 mmol) in dimethoxyethane (2 ml)/water (1 ml) was heated to 90° C. for 1.5 hr. The reaction mixture was cooled to room temperature, filtered and concentrated. The dark residue was purified by silica gel (50 g prepacked cartridge) using 0/100 to 8/92 MeOH/chloroform to provide 101 (12 mg).

Example 102

Procedure B



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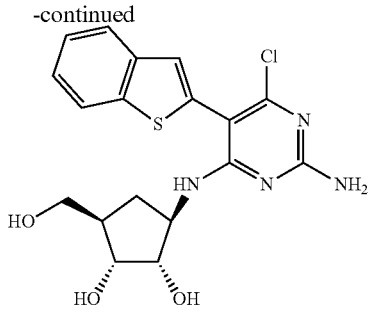
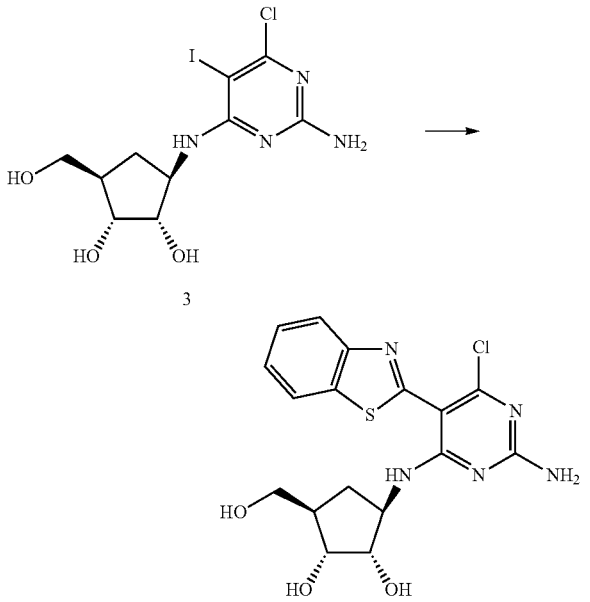


102

To a 0.5-2 ml microwave vial containing stir bar was added intermediate 3 (previously described, 40 mg, 0.1 mmol), thiophene-2-boronic acid (55 mg, 0.3 mmol), potassium carbonate (69 mg, 0.5 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium (II) (10 mg, 0.01 mmol) and dimethoxyethane (1 ml)/water (0.5 ml). The vial was sealed and subjected to microwave reaction at 120° C. for 15 min. Then the solvent was removed in vacuo, and the residue dissolved in chloroform/MeOH and flushed through a silicycle Si-carbonate cartridge (2 g). The cartridge was flushed with MeOH (~15 ml) and the filtrate was combined and concentrated. The crude residue was purified by reverse phase HPLC (Phenomenex Luna C-18 column) using water/MeCN (containing 0.1% formic acid) gradient which resulted in 16 mg of 102.

Example 105

Procedure C



3

105

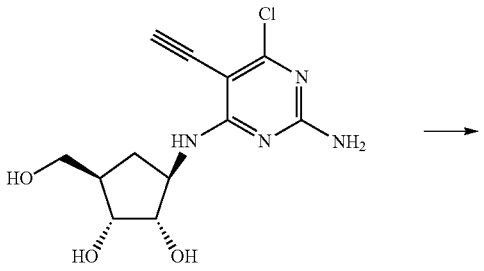
To a 0.5-2 ml microwave vial containing stir bar was added intermediate 3 (previously described, 60 mg, 0.15 mmol), tri-n-butylstannyl benzothiazole (128 mg, 0.3

mmol), copper iodide (12 mg, 0.06 mmol), dichlorobis (triphenylphosphine) palladium(II) (21 mg, 0.03 mmol), triethylamine (0.09 ml, 0.6 mmol) and DMF (1.5 ml). The vial was sealed and subjected to microwave reaction at 120° C. for 15 min. Then the solvent was removed in vacuo, and the residue dissolved in MeOH (~15 ml) and flushed through a silicycle Si-carbonate cartridge (2 g). The cartridge was flushed with MeOH (~15 ml) and the filtrate was combined and concentrated. The crude residue was purified by reverse phase HPLC (Phenomenex Luna C-18 column) using water/MeCN (containing 0.1% formic acid) gradient which resulted in 18 mg of 105 as a pale yellow solid.

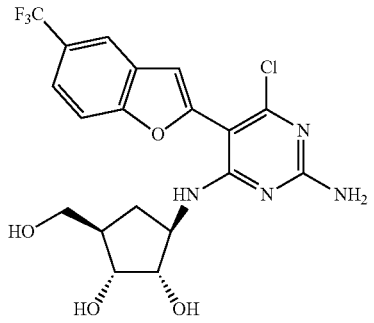
Note: Tetrakis(triphenylphosphine) palladium(0) can be used, instead of dichlorobis(triphenylphosphine) palladium (II), as the catalyst with similar results.

Example 108

Procedure D



3b

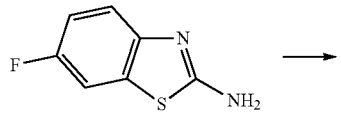


108

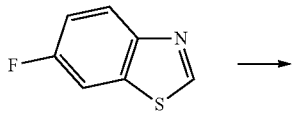
To a 0.5-2 ml microwave vial containing stir bar was added intermediate 3b (previously described by, 100 mg, 0.335 mmol), 2-bromo-4-trifluoromethyl phenol (121 mg, 0.5 mmol), copper iodide (26 mg, 0.134 mmol), tetrakis (triphenylphosphine) palladium(0) (77 mg, 0.07 mmol), triethylamine (0.19 ml, 1.34 mmol) and DMF (1.6 ml). The vial was sealed and subjected to microwave reaction at 120° C. for 10 min. Then the solvent was removed in vacuo, and the residue dissolved in MeOH (~15 ml). The solid was filtered off and the filtrate was flushed through a silicycle Si-carbonate cartridge (2 g). The cartridge was flushed with MeOH (~5 ml) and the filtrate was combined and concentrated. The crude residue was purified by reverse phase HPLC (Phenomenex Luna C-18 column) using water/MeCN (containing 0.1% formic acid) gradient which resulted in 41 mg of 108 as a pale yellow solid.

Example 110

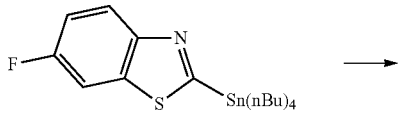
Procedure E



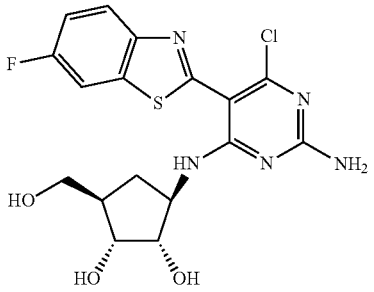
110a



110b



110c



110

Step 1:

Compound 110a was converted to compound 110b using literature described procedure (Chem. Pharm. Bull., 1998, 46 (4), 623-630.

Step 2:

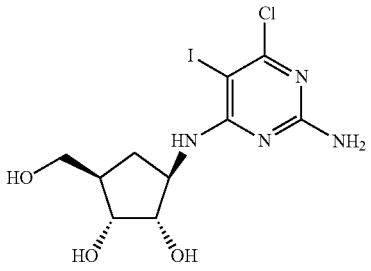
Compound 110b thus obtained (765 mg, 5 mmol) was dissolved in THF (10 ml) and cooled to −78° C. BuLi (1.6 M in hexanes, 3.15 ml, 5 mmol) was added dropwise over 15-20 minute period. Maintained reaction temperature at −78° C. for 1 hr and then added a solution of tri-n-butylstannyl chloride (1.63 g, 5 mmol) in THF (5 ml) over 15-20 min period. The reaction was warmed to −10° C. over 3 hrs. Then the reaction mixture was concentrated in vacuo. The crude material was dissolved in diethyl ether (~20 ml) and filtered. The filtrate was concentrated to provide 110c (2.16 g), which was used without any purification.

Step 3:

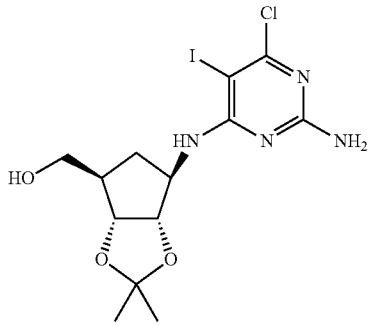
Treatment of 110c with 3 (0.15 mmol) followed procedures described above (Procedure C). After the reaction the residue was dissolved in MeOH and filtered thru 0.2 uM polypropylene filter cartridge. The filtrate was concentrated and the residue was purified as described above (see Procedure A) using reverse phase HPLC to obtain 37 mg of solid material. This solid was washed with acetone few times (4-5 ml each time) to provide 23 mg of 110.

Example 115

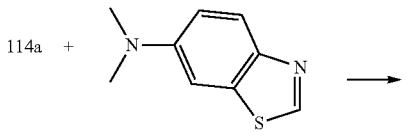
Procedure F



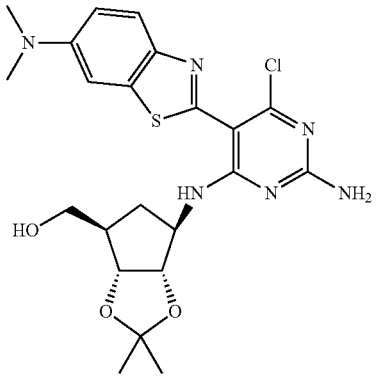
3



114a



114b



114

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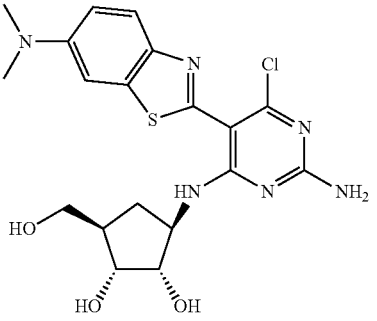


115

Step 1:

To a slurry of 3 (4.8 g, 12 mmol) in acetone at 0° C. was added 2,2-dimethoxypropane (2.97 ml, 24 mmol) followed by methanesulfonic acid (0.78 ml, 12 mmol). The reaction mixture was warmed to room temperature, overnight. Then the solvent was concentrated. To the residue was added saturated sodium bicarbonate solution (150 ml) and extracted with chloroform (2×100 ml). The organic layers were combined, washed with saturated sodium bicarbonate solution (150 ml), brine (200 ml), dried (Na_2SO_4), filtered and concentrated to afford 114a (5.48 g) which was taken further without any purification.

Step 2:

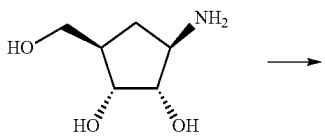
To a 5 ml microwave vial containing stir bar were added intermediate 114a (180 mg, 0.41 mmol), benzothiazole derivative 114b (140 mg, 0.79 mmol, 114b was prepared as described in literature; Synthesis, 2005, 4, 600-604), copper iodide (20 mg, 0.1 mmol), tetrakis(triphenylphosphine) palladium(0) (75 mg, 0.065 mmol), cesium carbonate (650 mg, 2 mmol) and DMF (4 ml). The vial was sealed and subjected to microwave reaction at 100° C. for 30 min. Then the reaction mixture was filtered thru 0.2 uM polypropylene filter cartridge and rinsed with EtOAc. Added water to the filtrate (50 ml) and extracted with EtOAc (2×50 ml). The organic layers were combined, washed with water (50 ml), brine (50 ml), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel (40 g prepacked cartridge) using 10/90 to 70/30 EtOAc/hexanes to provide 114 as a solid (26 mg). Some amounts of both the starting materials (114a and 114b) were also recovered.

Step 3:

The material obtained above, 114 (26 mg) was taken in MeOH (2 ml) and treated with aq 1N HCl (2 ml) at room temperature, overnight. The solvent was concentrated and the residue was dried under vacuum to provide 115 (26 mg, HCl salt).

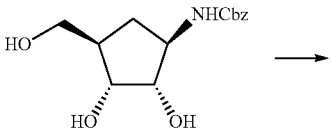
Examples 120 and 121

Procedure G

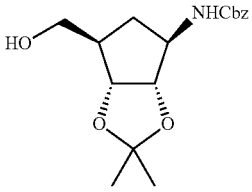


120a

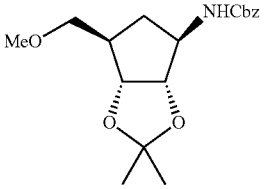
-continued



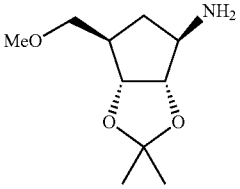
120b



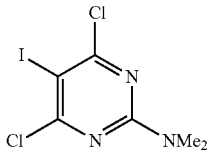
120c



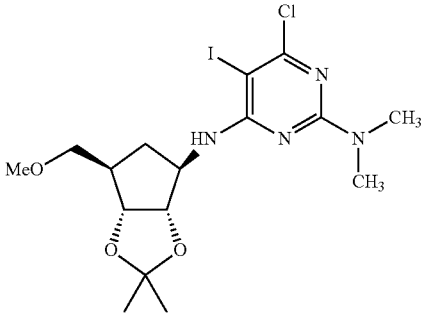
120d



120e

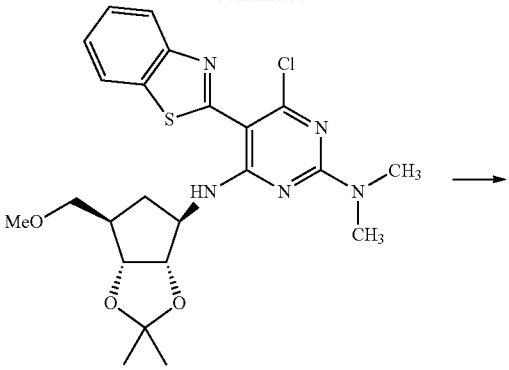


120f

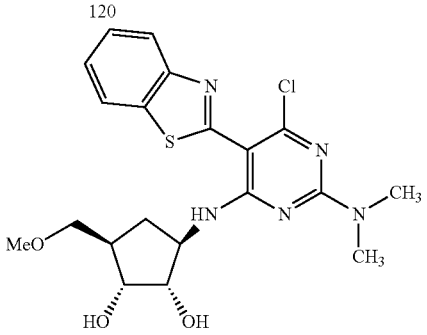


120g

-continued



120



121

Step 1:

To the carbasugar 120a (same as 2a, 1 g, 5.45 mmol) in dioxane (10 ml) and aq 1M sodium carbonate solution (15 ml) at room temperature was added Cbz-Cl (0.78 ml, 5.45 mmol). Stirred at room temperature for 5 hrs. Then concentrated the solvent. To the residue was added water (250 ml) and dichloromethane (150 ml). The org layer was separated and the aq layer was extracted with EtOAc (150 ml). The combined org layer was concentrated to approx half it volume and stored at 0° C. overnight. The precipitated solid was filtered off. The filtrate was concentrated and the residue was combined with the solid to provide 120b (610 mg).

Step 2:

To a slurry of 120b (590 mg, 2.1 mmol) in acetone (20 ml) at 0° C. was added 2,2-dimethoxy propane (0.52 ml, 4.2 mmol) and methanesulfonic acid (4 drops). The reaction mixture was warmed to room temperature, overnight. Then the solvent was concentrated. To the residue was added saturated sodium bicarbonate solution (75 ml) and extracted with EtOAc (75 ml). The organic layer was separated, washed with brine (50 ml), dried (Na_2SO_4), filtered and concentrated to afford 120c (680 mg) which was taken further without any purification.

Step 3:

To a solution of 120c (640 mg, 2 mmol) in acetonitrile (20 ml) was added iodomethane (2.1 ml, 34 mmol) and silver oxide (740 mg, 3.2 mmol). The reaction flask was covered with aluminum foil and refluxed overnight. The reaction mixture was cooled to room temperature, filtered through a pad of celite and rinsed with EtOAc. The combined filtrate was concentrated. The residue was purified by silica gel (80 g prepacked cartridge) using 10/90 to 60/40 EtOAc/hexanes to provide 120d (380 mg, white solid).

Step 4:

To a solution of 120d (370 mg, 1.12 mmol) in MeOH (20 ml) was added 10% palladium on carbon (catalytic amount) and the mixture was hydrogenated (using a balloon filled with hydrogen gas) at room temperature for 3 hrs. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to provide 120e (200 mg).

Step 5:

To 120e (190 mg, 1 mmol) and 120f (318 mg, 1 mmol, prepared as described below for 124d from appropriate starting material) in ethanol (10 ml) was added triethylamine (0.5 ml, 3.5 mmol) and heated to reflux, overnight. The reaction mixture was concentrated and purified by silica gel (40 g prepacked cartridge) using 25/75 to 75/25 of dichloromethane/hexanes to provide 120 g (205 mg).

Step 6:

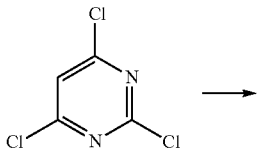
To 120 g (200 mg, 0.42 mmol) in dioxane (7 ml) was added a solution of tri-n-butylstannyl benzothiazole (350 mg, 0.84 mmol) in dioxane (3 ml). Then tetrakis(triphenylphosphine) palladium (0) (100 mg, 0.084 mmol), copper iodide (16 mg, 0.084 mmol) and triethylamine (0.24 ml, 1.68 mmol) were added and the mixture was heated to 100° C. for 1 hr. The reaction mixture was cooled to room temperature, filtered through 0.2 micron syringe filter and concentrated. The residue was purified by silica gel (40 g prepacked cartridge) using 0/100 to 50/50 EtOAc/hexanes to provide 120 as a solid (150 mg) which was slightly impure. This material was washed with MeOH (3×5-10 ml) to provide pure 120 (100 mg).

Step 7:

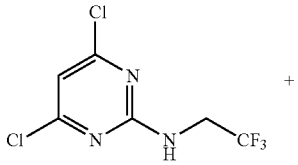
To 120 (95 mg, 0.194 mmol) in MeOH (6 ml) was added aq 1N HCl (9 ml) and dioxane (9 ml) and stirred at room temperature, overnight. The mixture was concentrated to give a solid residue that was washed with diethyl ether (2×10 ml). The resultant solid was dried to provide 121 (75 mg) as HCl salt.

Example 124

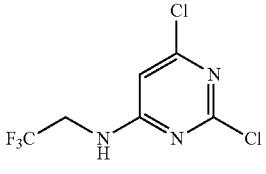
Procedure H



124a

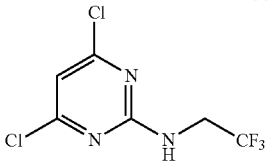


124b

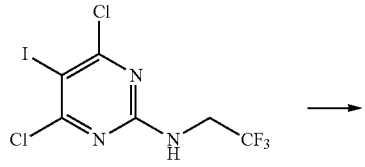


124c

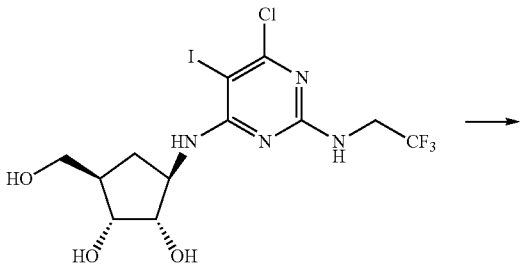
-continued



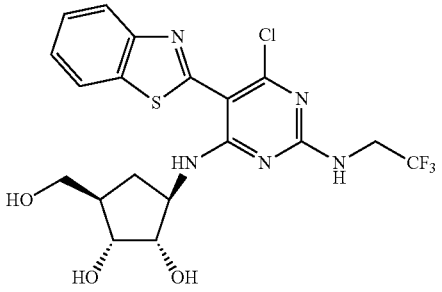
124b



124d



124e



124

Step 1:

To trichloropyrimidine 124a (2.9 ml, 25 mmol) in THF (25) at −15 C was added a solution of trifluoroethylamine (3.74 ml, 47.5 mmol) in THF (25 ml) over 1 hr. The reaction was warmed to 10 C over 4 hrs and stored at 8 C for approximately 48 hrs. Then water (150 ml) was added and extracted with EtOAc (2×150 ml). The combined organic layer was washed with brine (150 ml), dried (Na_2SO_4), filtered and concentrated. The residue (white solid, ~7 g, 124b and 124c) was stirred in heptane (100 ml) for 30 min at room temperature. The solid was filtered off, the filtrate was concentrated and purified by silica gel (120 g prepacked cartridge) using 0/100 to 50/50 EtOAc/hexanes to provide only 124b (1.04 g, white solid).

Step 2:

To 124b (1 g, 4.07 mmol) in acetic acid (10 ml) was added a solution of ICl (1.98 g, 12.2 mmol) in acetic acid (10 ml) over 30 minutes at room temperature. The mixture was stirred at room temperature, overnight. Added more ICl (2×~2 g) in acetic acid (5 ml) for complete conversion of starting material. The reaction was quenched by dropwise addition of ice cold saturated sodium bicarbonate solution (200 ml). Then added EtOAc (150 ml) and the mixture was stirred overnight. The organic layer was separated and the

aqueous layer was extracted with EtOAc (100 ml). The combined organic layer was washed with saturated sodium bicarbonate (200 ml), 10% aq. sodium bisulfite (2×200 ml), brine (150 ml), dried (Na_2SO_4), filtered and concentrated to afford 124d (1.68 g) as a white solid.

Step 3:

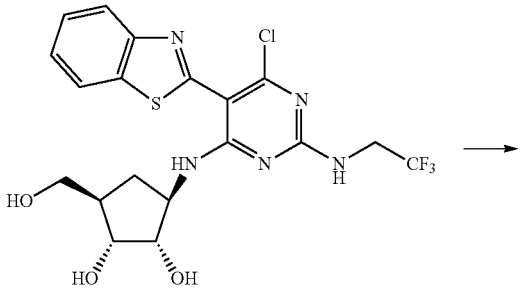
The above obtained intermediate 124d (1.65 g, 4.44 mmol) in EtOH (25 ml) was treated with carbasugar 120a (4.40 mmol) and triethylamine (2.2 ml, 15.54 mmol). The mixture was refluxed, overnight. Then solvent was evaporated, and the residue was washed with water several times to afford 124e (1.88 g) as a solid.

Step 4:

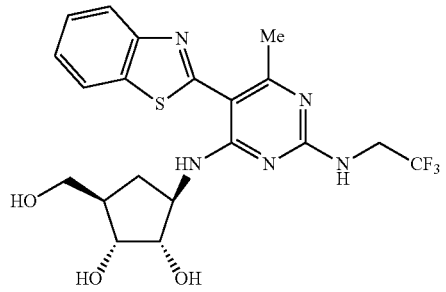
To a mixture of 124e (482 mg, 1 mmol), tetrakis(triphenylphosphine) palladium (0) (231 mg, 0.2 mmol), copper iodide (38 mg, 0.2 mmol), triethylamine (0.56 ml, 4 mmol) and tri-n-butylstannyl benzothiazole (848 mg, 2 mmol) in dioxane (20 ml) were added and the mixture was heated to 100 C. for 1 hr. The reaction mixture was cooled (RT to 50 C), diluted with EtOAc and filtered thorough a pad of celite. The filtrate was concentrated. The solid residue was washed with dichloromethane/MeOH (minimum amount) and the filtrate was discarded. The solid was then washed with 1:1 dichloromethane/MeOH (few times) and filtered. The solid (258 mg) was essentially product, 124 (by mass spectral analysis). The filtrate was concentrated and purified by silica gel (50 g prepacked cartridge) using 0/100 to 12/88 MeOH/dichloromethane to afford a yellow-brown solid (42 mg) that was washed with cold acetone (3×~2 ml) to provide additional 124 (21 mg, pale yellow solid).

Example 125

Procedure I



124



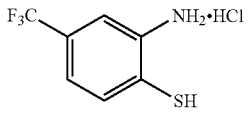
125

A mixture of 124 (122 mg, 0.25 mmol), methyl boronic acid (45 mg, 0.75 mmol), potassium carbonate (173 mg) and dichloro(bis-triphenylphosphine)palladium II (35 mg, 0.05 mmol) in dioxane (6 ml)/water (3 ml) was heated to 100-110 C for 2 hr. The solvent was evaporated and the residue was washed with water. The remaining black residue was purified by silica gel (50 g prepacked cartridge) using 0/100 to 12/88 MeOH/dichloromethane to provide 125 (31 mg) as an off-white solid.

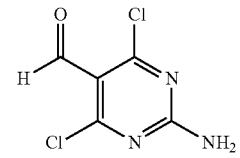
(Note: Tetrakis(triphenylphosphine) palladium (0) can be used instead of dichloro(bis-triphenylphosphine)palladium II with similar results).

Example 112

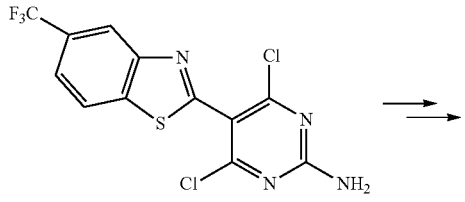
Procedure J



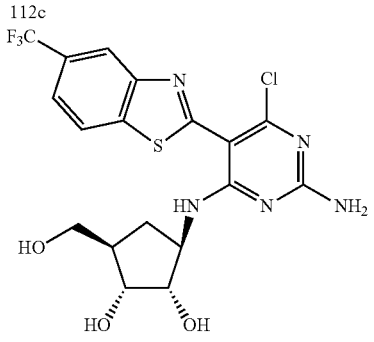
112a



112b



112c



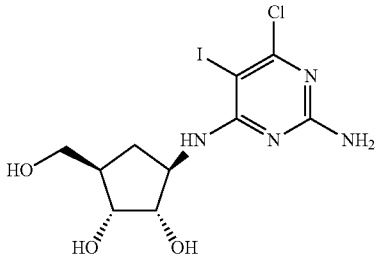
112

To a mixture of 112a (253 mg, 1.1 mmol) and 112b (192 mg, 1.0 mmol) was added DMF (20 ml) and the reaction mixture was stirred at room temperature overnight. Then poured the mixture into ice/saturated sodium bicarbonate solution (40 ml). The precipitated solid was collected by filtration and washed with water. The solid was taken in DMF (10 ml) and added gl. acetic acid (10 drops). The reaction mixture was stirred at room temperature overnight and processed as above. The solid thus obtained (223 mg) was taken in dichloromethane (10 ml) and treated with DDQ (138 mg, 0.6 mmol) at room temperature for 1 hr. The

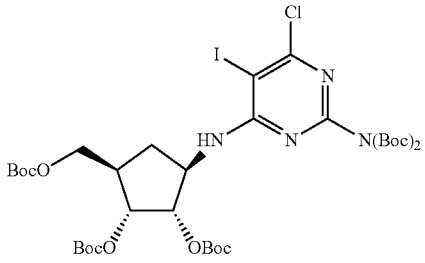
reaction mixture was diluted with chloroform (30 ml) and washed with saturated sodium bicarbonate solution (50 ml). Separated the organic layer, and the aqueous layer was extracted with EtOAc (50 ml). Combined the organic layers, dried (Na_2SO_4), filtered and concentrated to provide 112c which was taken further without any purification. Conversion of 112c (0.6 mmol) to required product 112 followed procedures described above (Procedure H, Step 3). Crude 112 thus obtained was treated with excess di-tert-butyl dicarbonate (440 mg), catalytic DMAP (10 mg) in THF (8 ml) at room temperature, overnight. The reaction mixture was processed using EtOAc (50 ml) and brine (50 ml). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. The residue was purified using silica gel (prepacked, 40 g cartridge) with 20/80 to 70/30 of EtOAc/hexanes. This resulted in 32 mg of product containing two t-boc groups. This material was deprotected with 4M HCl in dioxane (5 ml) at room temperature, overnight. The reaction mixture was concentrated, and the residue purified using silica gel (prepacked, 12 g cartridge) with 1/99 to 12/88 of MeOH/chloroform to provide 6 mg of 112 as a light brown solid.

Example 403 and 404

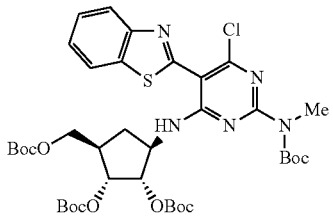
Procedure K



3

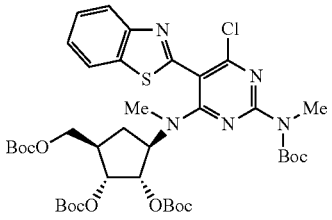


403a

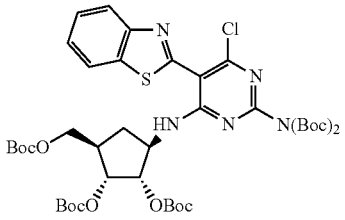


403c

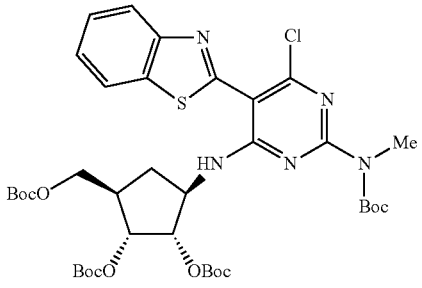
and



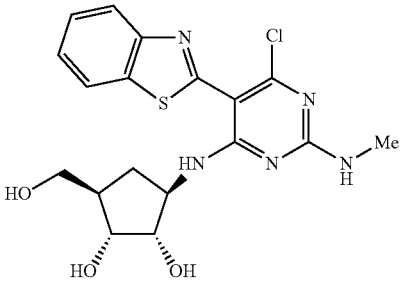
404a



403b



403c



403-HCl Salt

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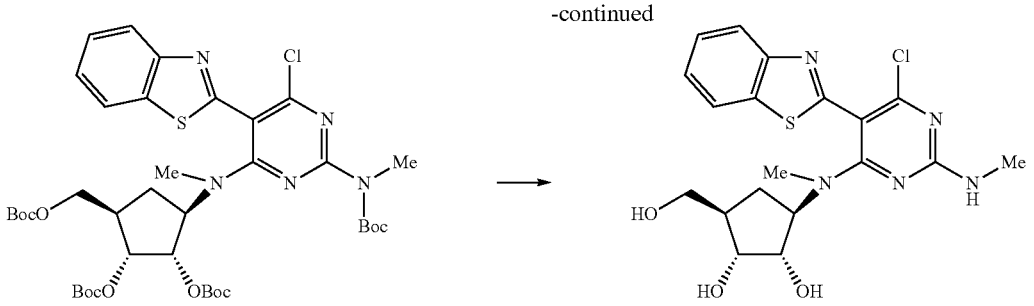


404a 404-HCl Salt

Di-tert-butyl dicarbonate (0.474 g) was added to a stirred mixture of the triol (3; 0.134 g) and DMAP (0.08 g) in THF (5 ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. NaHCO3, water, dried (MgSO4). The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using hexanes; EtOAc; 5:1 as eluent to provide the desired penta-Boc derivative (403a; 0.226 g) as a white solid.

Triethylamine (0.124 ml) was added to a mixture of 2-tributylstannylbenzothiazole (0.200 g), the iodide (403a; 0.200 g), dichlorobis(triphenylphosphine)palladium(II) (0.032 g), copper(I) iodide (0.016 g) in dioxane (3 ml) and the resulting reaction mixture was heated to 100 C. (oil bath temp.) for a period of 1 h. After cooling, EtOAc was added and the suspension was filtered through a pad of celite and the solid was thoroughly washed with EtOAc. The filtrate was washed with water, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using hexanes: EtOAc; 5:1 as eluent to provide the desired benzthiazole (403b; 0.201 g) as a light-brown solid.

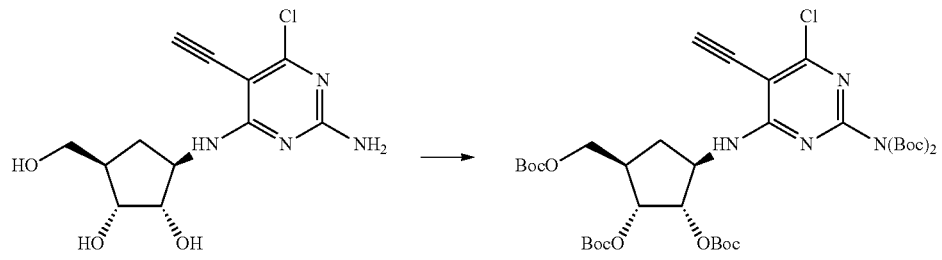
Sodium hydride (0.008 g of a 60% dispersion in mineral oil), followed by iodomethane (0.047 g) were added to a stirred solution of 403b (0.200 g) in anhydrous THF (3 ml). The resulting mixture was stiffed for 2 h., and additional portions of sodium hydride (0.008 g) and iodomethane (0.047 g) were added and the reaction was stirred overnight. The reaction mixture was partitioned between EtOAc and water and AcOH (~1 ml) was added. The organic phase was separated, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography to give 403c (0.007 g); 1H NMR ($CDCl_3$) δ1.43 (s, 9H), 1.46 (s, 9H), 1.49 (s, 9H), 1.50-1.55 (m, 1H), 1.56 (s, 9H), 2.62-2.76 (m, 2H), 3.40 (s, 3H), 4.20 (d, 2H, J=5.3 Hz), 4.60-4.66 (m, 1H), 5.02-5.06 (m, 1H), 5.23-5.27 (m, 1H), 7.39-7.44 (m, 1H), 7.47-7.52 (m, 1H), 7.92 (d, 1H, J=8.0 Hz), 8.09 (d, 1H, J=8.0 Hz) and 11.22 (d, NH, J=5.8 Hz), MH+, 822.28 and 404a (0.038 g); ^1H NMR ($CDCl_3$) δ1.44 (s, 9H), 1.46 (s, 9H), 1.47-1.49 (m, 1H), 1.48 (s, 9H), 1.55 (s, 9H), 2.12-2.22 (m, 1H), 2.36-2.46 (m, 2H), 2.58 (s, 3H), 3.41 (s, 3H), 4.01-4.11 (m, 2H), 4.84-4.90 (m, 1H), 5.02-5.11 (m, 2H), 7.41-7.46 (m, 1H), 7.50-7.55 (m, 1H), 7.89 (d, 1H, J=8.1 Hz), and 8.10 (d, 1H, J=8.1 Hz), MH+, 836.30.

2N HCl in ether (2 ml) was added to 403c (0.007 g) and the mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure to give 403-HCl salt (0.006 g).

2N HCl in ether (2 ml) was added to 404a (0.038 g) and the mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure to give 404-HCl salt (0.022 g).

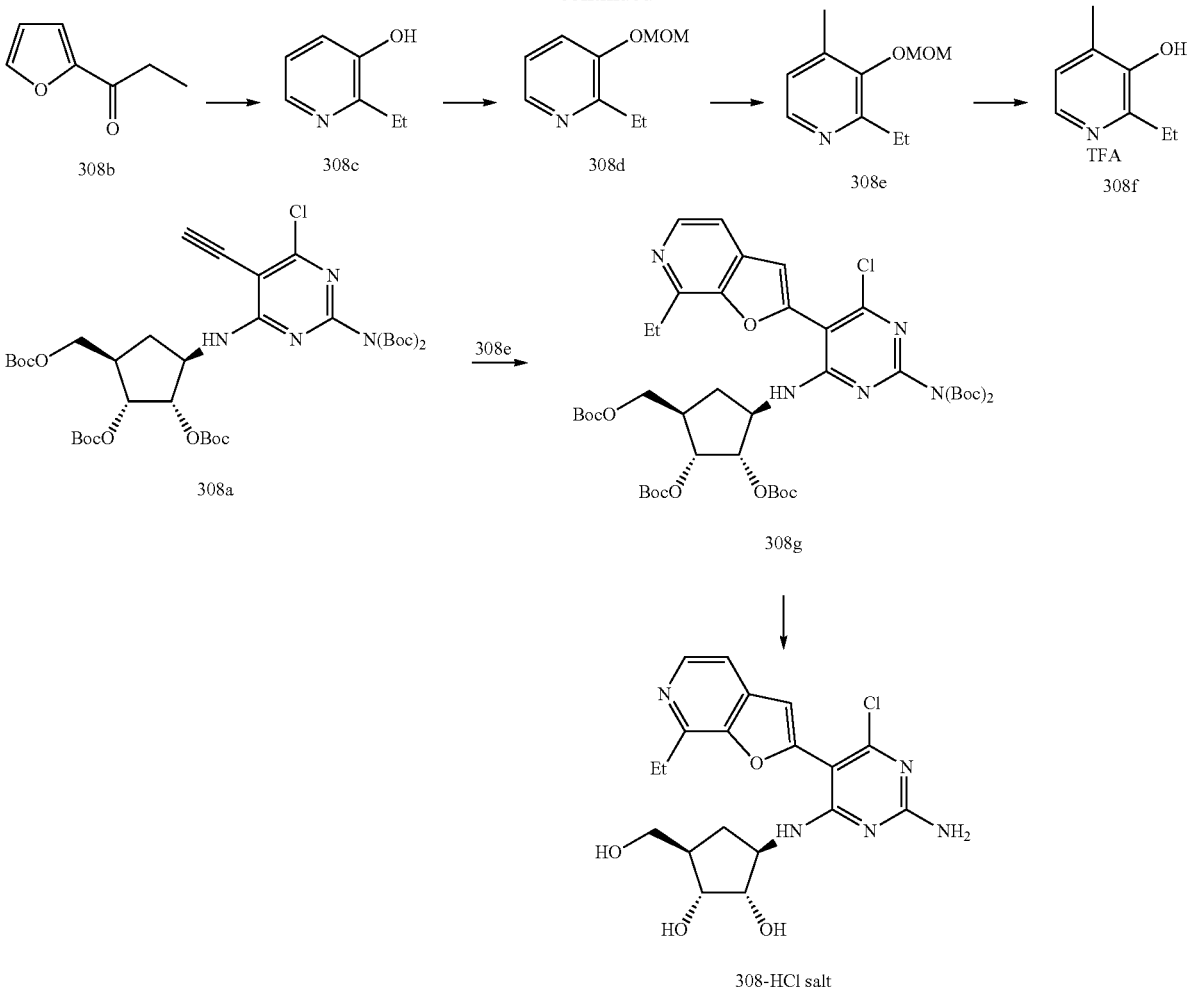
Example 308

Procedure L



3b 308a

-continued



Di-tert-butyl dicarbonate (0.474 g) was added to a stirred mixture of the triol (3b; 0.100 g) and DMAP (0.08 g) in THF (5 ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. NaHCO3, water, dried (MgSO4). The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using hexanes; EtOAc; 10:3 as eluent to provide the desired penta-Boc derivative (308a; 0.210 g) as a white solid.

Ammonia was bubbled into a suspension of ammonium chloride (3.00 g) and the ketone (308b; 6.20 g) in ethanol (15 ml) in a pressure bottle for 10 min. The bottle was sealed and heated in an oil bath at 200 C. overnight. After cooling, the volatiles were removed under reduced pressure and the residue partitioned between methylene chloride and continuously extracted overnight. The volatiles were removed under reduced pressure and the crude reaction product was purified by silica gel column chromatography using hexanes; EtOAc (5:1) to give the desired pyridol (308c; 0.701 g) as a brown solid.

Chloromethyl methyl ether (0.46 ml) was added dropwise to a stirred mixture of 308c (0.65 g), Hunigs base (1.41 ml) in anhydrous dichloromethane (10 ml), while cooled in an ice bath, under an atmosphere of nitrogen. The resulting mixture was allowed to reach room temperature, overnight. Solid sodium bicarbonate was added and the suspension was partitioned between methylene chloride and water. the organic phase was separated, dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using hexanes; EtOAc (1:10) as eluent to give the desired ether 308d (0.59 g) as a yellow oil.

To a solution of the ether (308d; 0.55 g) in anhydrous THF (10 ml) at −78 C, under an atmosphere of nitrogen was added n-Butyl lithium (1.5 ml of a 2.5M solution in hexanes). The resulting mixture was stirred at this temperature for 1 h. and a solution of iodine (0.92 g) in anhydrous THF (5 ml) was added. After stirring for a further 1 h., a 1M aq. solution of NH4Cl was added and the suspension was allowed to warm to room temperature before partitioning between EtOAc and water. The organic phase was separated, washed with 10% aq. sodium thiosulfate, water, dried (MgSO4) and the volatiles were removed under reduced pressure. The solid was subjected to silica gel column chromatography (hexanes; EtOAc; 1:10) to provide the desired iodide 308e (0.926 g) as a white solid.

To a solution of the acetal (308e; 0.900 g) in dichloromethane (8 ml) was added TFA (2 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was

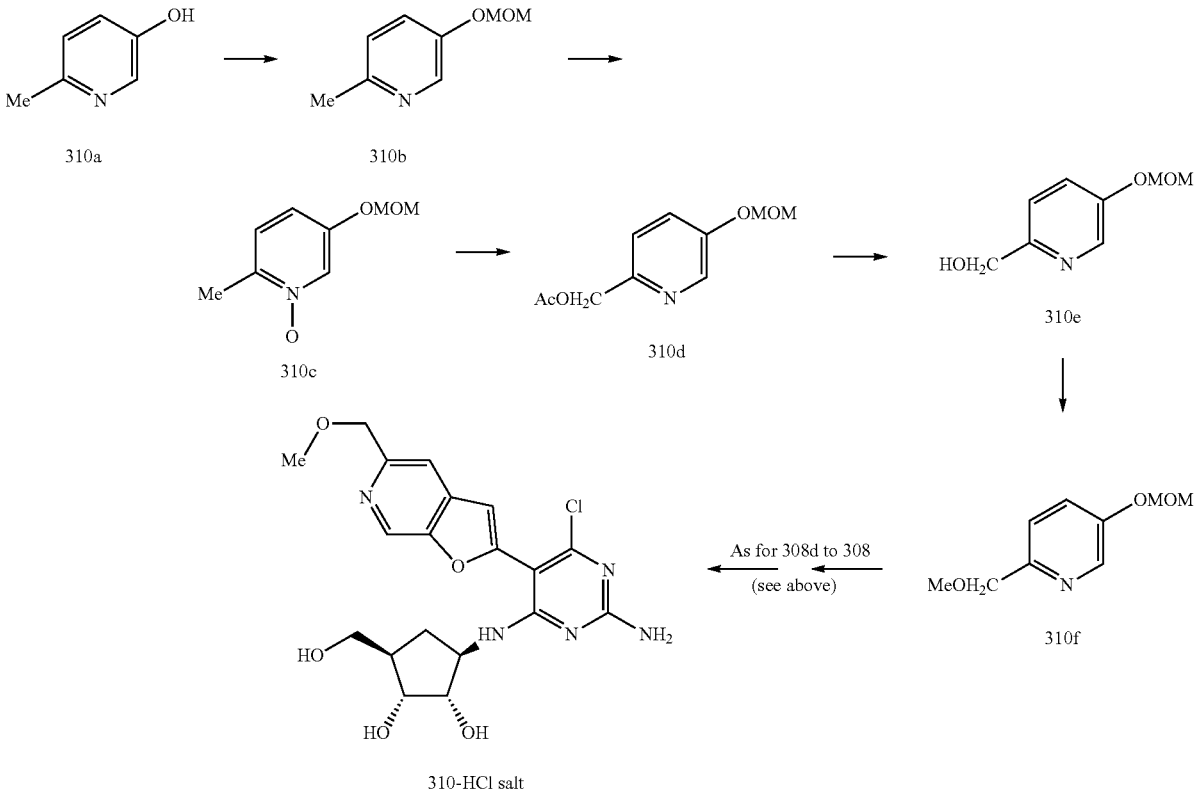
stirred overnight before removing the volatiles under reduced pressure to give the salt 308f (1.09 g) as a light-brown oil.

To the acetylene (308a 0.114 g), the iodide (308f; 0.077 g), Tetrakis(triphenylphosphine) palladium (0) (0.040 g), copper (I) iodide (0.013 g) in dioxane (3 ml) was added triethylamine (0.100 ml) and the resulting mixture was heated to 100 C (oil bath temp.), under an atmosphere of nitrogen, for a period of 1 h. After cooling, EtOAc was added and the mixture was filtered through a pad of celite and the solid was thoroughly washed with EtOAc. The combined filtrate was washed with 10% aq. HCl, water, dried (MgSO4) and the volatiles removed under reduced pressure. The crude reaction product was purified by silica gel using hexanes:EtOAc (10:3) as eluent to give the desired azabenzofuran (308 g; 0.091 g) as a white solid.

To the pyridylfuran (308g; 0.080 g) was added 4M HCl in dioxane (3 ml) and the resulting solution was allowed to stand at room temperature overnight. the volatiles were removed under reduced pressure to give the triol (308).

Example 310

Procedure M



Chloromethyl methyl ether (0.78 ml) was added dropwise to a stirred mixture of 310a (1.00 g), Hunigs base (2.41 ml) in anhydrous dichloromethane (30 ml), while cooled in an ice bath, under an atmosphere of nitrogen. The resulting mixture was allowed to reach room temperature, overnight. Solid sodium bicarbonate was added and the suspension was partitioned between methylene chloride and water. The organic phase was separated, dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using hexanes; EtOAc (1:10) as eluent to give the desired ether 310b (0.44 g) as a yellow oil.

MCPBA (0.515 g of 77% pure material) was added to the ether (310b; 0.32 g) and sodium bicarbonate (0.528 g) in dichloromethane (5 ml) while cooled in an ice bath. the resulting mixture was stiffed for 1.5 h. and 5% aq. sodium carbonate was added and the mixture partitioned between methylene chloride and water. The organic phase was separated and the aqueous phase further extracted with methylene chloride. The combined organic phases was dried (MgSO4) and the volatiles were removed under reduced pressure to give the N-oxide (310c) used in the next step without purification.

Acetic anhydride (0.237 ml) was added to a mixture of the N-oxide (310c; all material from the previous step) Hunigs base (0.474 ml) in dioxane and the resulting mixture was heated to reflux, overnight, under an atmosphere of nitrogen. After cooling, the reaction was partitioned between methylene chloride and water. The organic phase was separated, dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired ester (310d; 0.340 g) as a colourless oil.

Potassium carbonate (0.050 g) was added to a solution of the ester (310d; 0.34 g) in methanol (5 ml) at room temperature and the resulting mixture was stirred for a period of 4 h. The volatiles were removed under reduced pressure and the residue partitioned between methylene chloride and water. The organic phase was separated and the aqueous phase further extracted with methylene. The organic phases

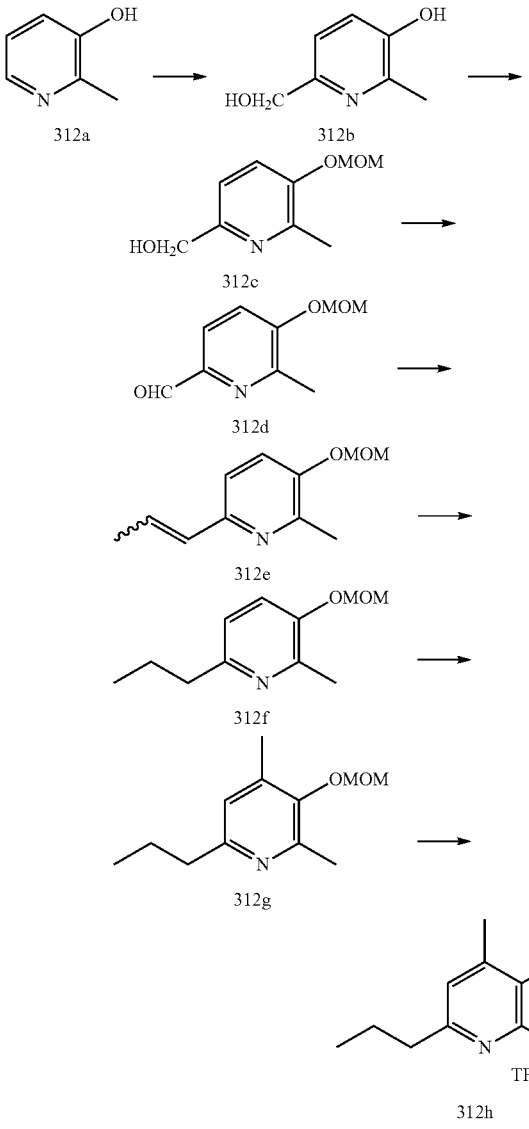
were combined, dried (MgSO4) and concentrated. Gave the alcohol (310e; 0.229 g).

Iodomethane (0.101 ml) was added dropwise to a stirred suspension of the alcohol (310e; 0.229 g) and sodium hydride (0.081 g of a 60% dispersion in mineral oil) in anhydrous THF (5 ml) while cooled in an ice bath under an atmosphere of nitrogen and the resulting mixture was allowed to warm to room temperature over a period of 3 days. The reaction mixture was partitioned between methylene chloride and water. The organic phase was separated, dried (MgSO4). The residue was purified by silica gel column chromatography to give the desired ether (310f; 0.201 g) as a yellow oil.

Using the same series of transformation as described above for the conversion of 308d to 308, 310f was used for the preparation of 310.

Example 312

Procedure N



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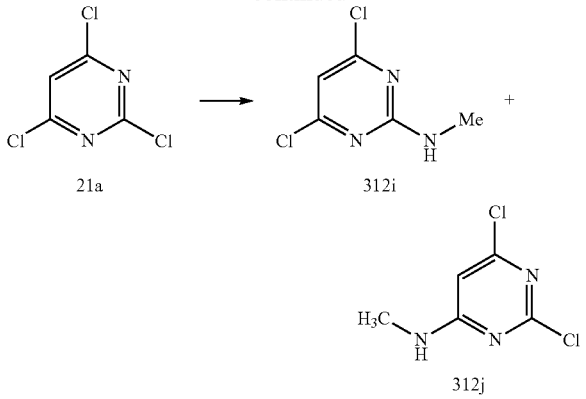

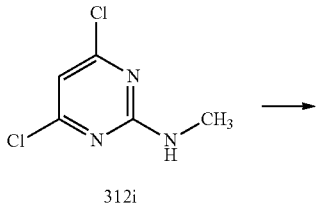

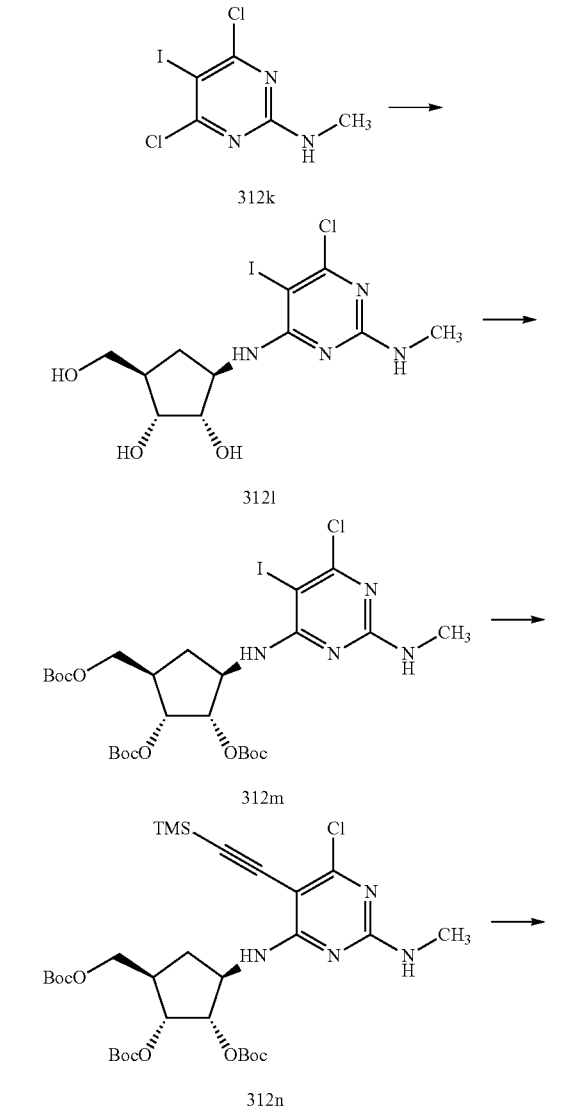

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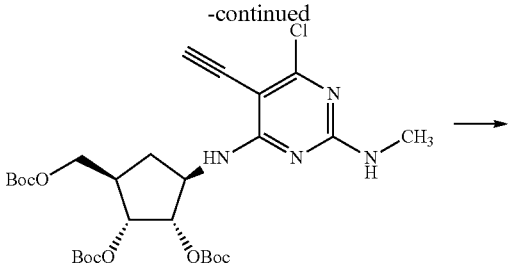
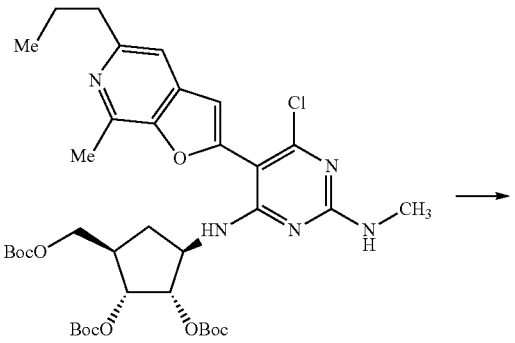
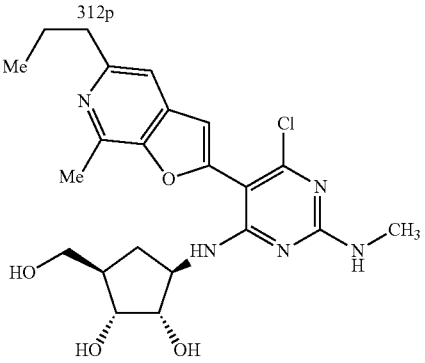


312o



312p



312-HCl Salt

A mixture of 3-hydroxy-2-methylpyridine (21a; 3.64 g), 10% aq. NaOH (13 ml) and 40% formalin (3 ml) in water (10 ml) was refluxed for 2 h. An additional portion of formalin (3 ml) was added and the resulting mixture was heated to reflux for an additional 2 h. The reaction mixture is acidified with acetic acid, filtered and the filtrate evaporated to dryness. The residue was purified by silica gel column chromatography using methylene chloride: MeOH (20:1) as eluent to give the desired diol (312b; 3.00 g).

To the diol (312b; 1.00 g) and potassium t-butoxide (0.888 g) in anhydrous THF (20 ml) was added chloromethyl methyl ether (0.65 ml) and the resulting mixture stirred at room temperature overnight. The volatiles were removed under reduced pressure and to the residue was added methylene chloride followed by sodium bicarbonate. The suspension was filtered and the filtrate concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using methylene chloride: MeOH (48:1) to give the desired acetal (312c; 0.87 g).

The Dess-Martin periodinane (0.76 g) was added to a stirred solution of the alcohol (312c; 0.30 g) and the resulting mixture was stirred at room temperature for 3 h. The reaction was diluted with EtOAc and washed with 5% aq. sodium sulfite, sat aq. sodium bicarbonate, dried (MgSO4) and the volatiles removed under reduced pressure. The crude aldehyde (312d) was used in the next step without purification.

KHMDS (6.6 ml of a 0.5M solution in toluene) was added to a suspension of ethyltriphenylphosphonium bromide (1.23 g) in anhydrous THF (10 ml) at room temperature, under an atmosphere of nitrogen. After stirring for 0.5 h, the orange suspension was cooled to −78 C before the addition of the aldehyde (312d; all material from the previous step) in anhydrous THF (@2 ml). The reaction was maintained at this temperature for 0.5 h., and allowed to warm to room temperature and stirred for a further 0.5 h. The reaction was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:20) to give the alkenes (312e; 0.095 g).

10% Pd/C was added to a ethanol (3 ml) solution of the alkenes (312e; 0.095 g) and the black suspension was placed under an atmosphere of hydrogen (balloon), overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the dialkylpyridine (312f; 0.071 g).

The pyridine (312f; 0.064 g) was dissolved in anhydrous THF (1 ml) was cooled to −78 C, under an atmosphere of nitrogen and a solution of nBuLi (0.16 ml of a 2.5M solution in hexanes) was added and the resulting reaction mixture maintained at this temperature for 1 h. Iodine (0.108 g) in anhydrous THF (1 ml) was added and the reaction was stirred for a further 1 h, before 1M aq. ammonium chloride. After warming to room temperature the mixture was partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:10) as eluent to give the iodide (312g; 0.0806 g), containing a small amount of starting material.

To the iodide from the previous step (312g; 0.080 g) in dichloromethane (5 ml) was added TFA (1 ml) and the mixture left to stand a room temperature overnight. The volatiles were removed under reduced pressure to give the salt (312h).

A solution of methylamine (57 ml of a 2M solution in THF) was added dropwise to a stirred solution of trichloropyrimidine (124a; 10.00 g) in anhydrous THF (80 ml) at −20 C, under an atmosphere of nitrogen and the reaction was maintained at this temperature for 0.5 h. The volatiles were removed under reduced pressure and the residue partitioned between methylene chloride and 10% aq. NaOH. The organic phase was separated, washed with water, dried (MgSO4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc; hexanes (1:20) as eluent to give the desired product (312i; 4.05 g) as a white solid. The relatively more polar isomer (312j) was set aside at this time.

Iodine monochloride (12.08 g) was dissolved in acetic acid and added dropwise to the aminopyrimidine (312i; 4.00 g) and the resulting mixture was stirred overnight at room temperature. EtOAc and sat aq. sodium bicarbonate was added. Additional excess sodium bicarbonate was added and the mixture was poured in to a mixture of 10% aq. sodium thiosulfate and EtOAc. The organic phase was separated,

washed with water, dried (MgSO4) and concentrated under reduced pressure. Gave the desired iodopyrimidine (312k; 5.97 g) as a white solid.

Triethylamine (1.61 ml) was added to a mixture of the 'carbasugar hydrochloride' (120a; 0.606 g) and pyrimidine (312k; 1.00 g) in ethanol (50 ml) and the resulting mixture was heated to reflux overnight, under an atmosphere of nitrogen. After cooling, the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methylene chloride; methanol (20:1) as eluent to give the desired product (312l; 1.32 g) as a white sold.

To the triol (312l; 0.56 g) in anhydrous THF (25 ml) was added di-tert-butyl dicarbonate (1.42 g) followed by DMAP (0.040 g). the resulting mixture was stirred at room temperature, under an atmosphere of nitrogen overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography to give the tri-Boc (312m; 0.79 g) as a white solid.

Copper(I) iodide (0.014 g) followed by dichlorobis(triphenylphosphine)palladium(II) (0.026 g) were added to a stirred mixture of the tri-Boc (312m; 0.261 g), triethylamine (0.203 ml) and trimethylsilylacetylene (0.152 ml) in anhydrous dioxane (4 ml) and the resulting mixture was heated to 50 C, under an atmosphere of nitrogen, overnight. After cooling, further portion of the palladium catalyst (0.026 g), copper(I) iodide (0.014 g) and the mixture heated for a further period of 1 h. The volatiles were removed under reduced pressure and EtOAc was added. The suspension was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The combined filtrate was washed with 10% aq. HCl, water, dried (MgSo4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired acetylene (312n; 0.0201 g) as a white solid.

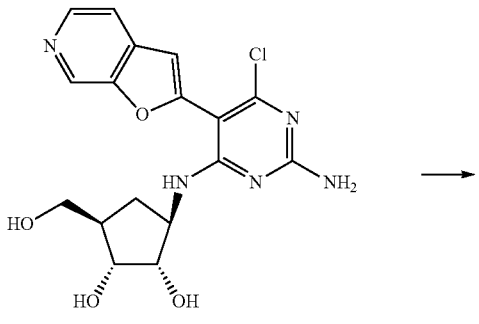
To the silane (312n; 0.181 g) in acetonitrile (3 ml) was added tetraethylammonium fluoride hydrate and the resulting mixture was stirred at room temperature for 2 h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using EtOAc:hexanes (15:85) to give the desired product (3120; 0.121 g) as a white solid.

Copper(I) iodide (0.013 g) followed by tetrakis(triphenylphosphine) palladium (0) (0.040 g) were added to a mixture of the phenol (312h; all the material derived from 312o described above) triethylamine (0.113 ml) and the acetylene (2130; 0.100 g) in dioxane (3 ml) and the resulting mixture was heated to 100 C (oil bath temp.), under an atmosphere of nitrogen for 1 h. After cooling, EtOAc was added and the suspension was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The combined filtrate was washed with 10% Aq. HCl, water, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc; hexanes (1:5) as eluent to give the desired azabenzofuran (312p; 0.0623 g) as a white solid.

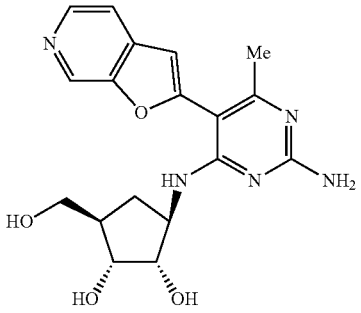
To the tri-Boc (312p; 0.060 g) was added 4M HCl in dioxane and the resulting solution was allowed to stand at room temperature overnight. The volatiles were removed under reduced pressure to give the triol (312; 0.036 g) as a light-brown solid.

Example 418

Procedure O



5

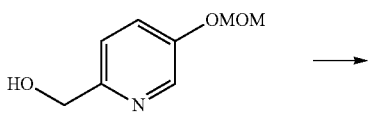


418

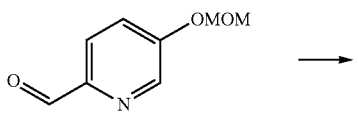
Dichlorobis(triphenylphosphine)palladium(II) (0.018 g) was added to a mixture of the chloride (5; 0.050 g) methylboronic acid (0.022 g) and potassium carbonate (0.088 g) in a mixture of dioxane (2 ml) and water. The resulting mixture was heated to 120 C, for 2 h., under an atmosphere of nitrogen. After cooling, methanol was added and the suspension was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel plate chromatography using methylene chloride:methanol (5:1) as eluent to give the desired alkylated product (418; 0.006 g). Some impure material was also obtained but was not pursued at this time,

Intermediate 516d

Procedure P



310e



516a

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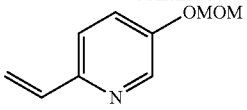
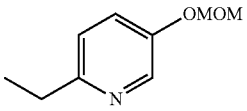
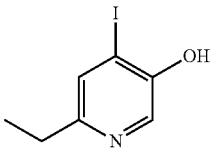


516b



516c



516d

Step 1:

Compound 310e (synthesis described in Procedure M, 1.4 g, 8.38 mmol) was dissolved in methylene chloride (20 mL) and Dess Martin Periodinane (3.9 g, 9.2 mmol) was added. The reaction was stirred for 2 hours and then quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to provide the aldehyde 516a (1.4 g) that was used without purification.

Step 2:

Methylphosphonium bromide (6.0 g, 16.76 mmol) was suspended in THF (20 mL) and a 0.5M solution of KHMDS in toluene (33 mL, 16.5 mmol) was added. The reaction mixture was stiffed for twenty minutes and then cooled in an ice bath. The aldehyde 516a (1.4 g, 8.38 mmol) from step 1 was added dropwise in THF (10 mL) and the reaction was stiffed for 1 hour and then quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by column chromatography (80% hexanes/ethyl acetate) to provide the desired alkene 516b (1.2 g).

Step 3:

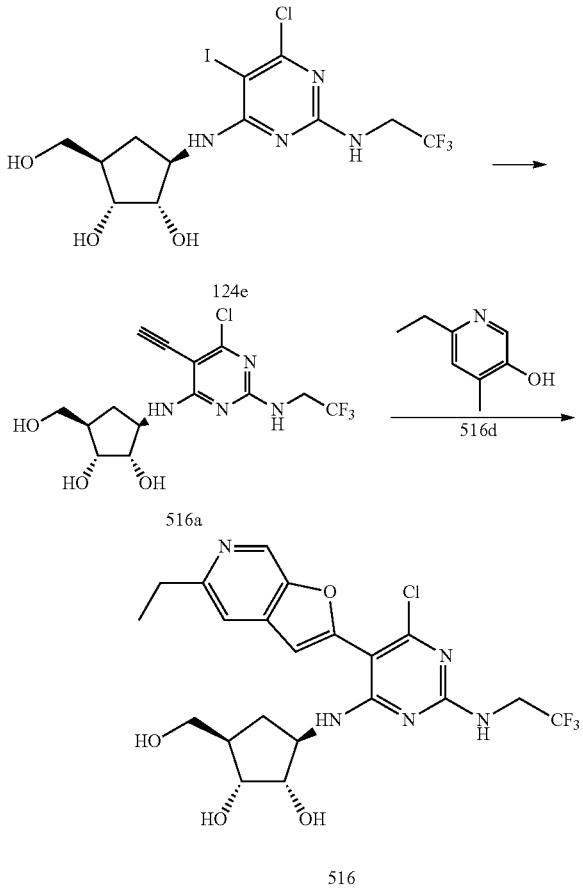
The alkene 516b from Step 2 (1.2 g, 7.36 mmol) was dissolved in methanol (15 mL). 10% Pd—C was added under an inert atmosphere. The reaction mixture was purged with hydrogen and stirred under a hydrogen atmosphere (1 atm) for 12 hours. The reaction mixture was filtered over celite and the solvent was removed under reduced pressure to provide the desired product 516c (1.0 g) that was used without purification.

Step 4:

Compound 516d was prepared from 516c using procedures similar to those described in Procedure L.

Example 516

Procedure Q



124e

516a

516d

516

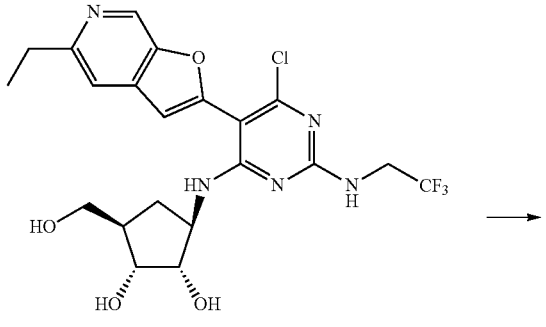
Step 1:

Compound 516a was prepared from 124e as described in general procedure A2.

Step 2:

Compound 516a and 516d were reacted using chemistry described in general procedure A2 (example 5) to provide compound 516.

Procedure R:



516

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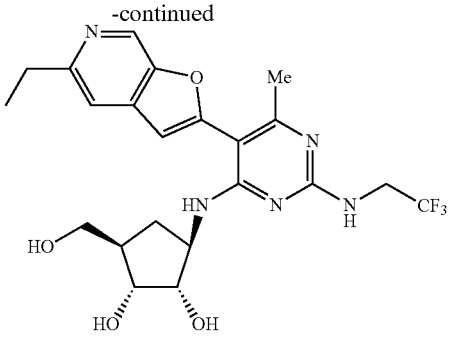


517

Compound 517 was prepared from compound 516 using chemistry described in Procedure O.

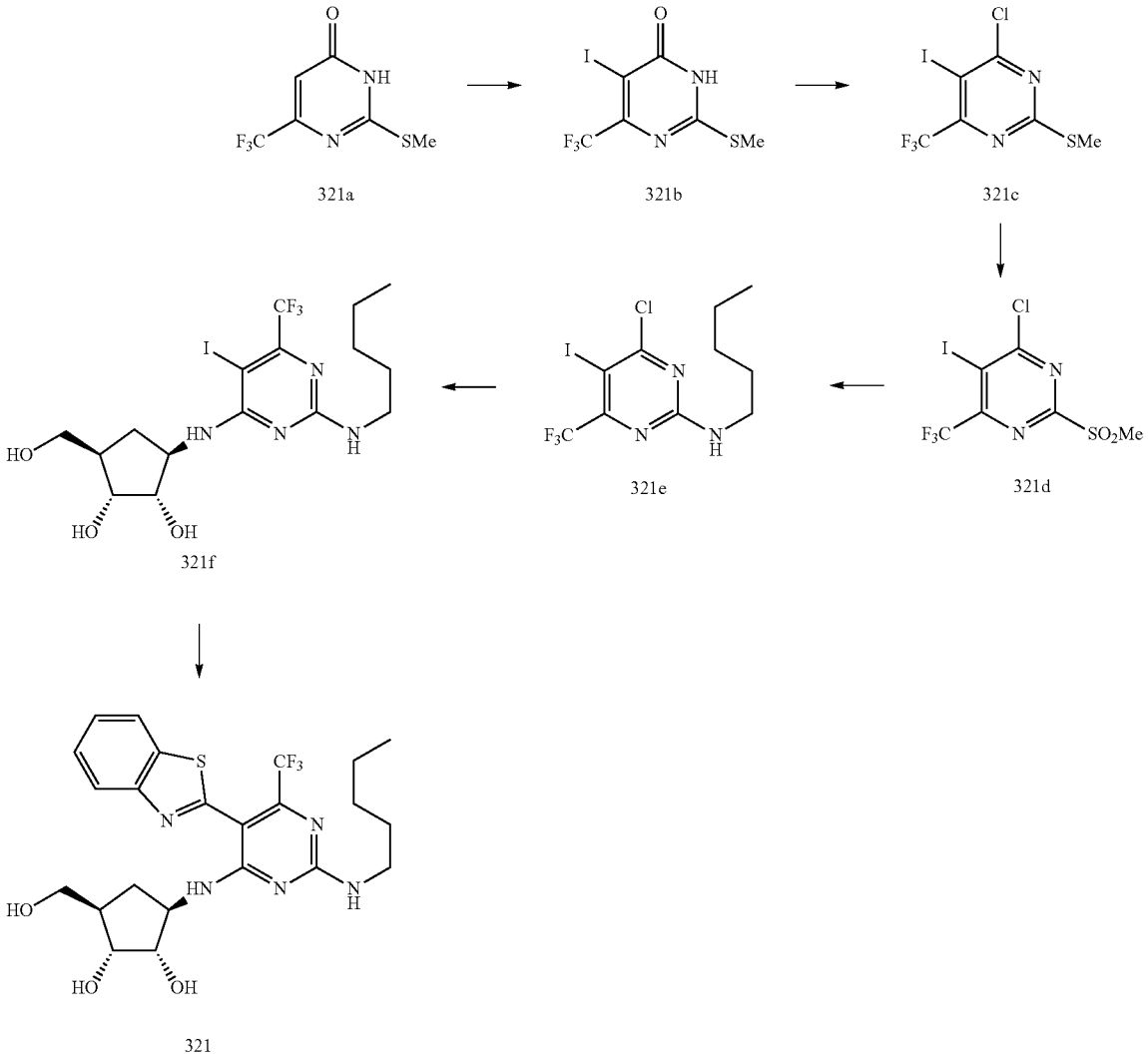
Example 321

Procedure S

N-Iodosuccinimide (5.92 g; 26 mmol) was added to a stirred solution of the pyrimidone (321a; 5.00 g; 24 mmol; Aldrich) in acetonitrile (50 ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen, for 4 h. After cooling, the volatiles were removed under reduced pressure. The residue was partitioned ethyl acetate and 10% aq. sodium thiosulfate. The organic phase was separated, washed with water, dried (MgSO4) and the volatiles were removed under reduced pressure to provide the iodide (321b; 5.56 g) as a yellow solid which was used without purification.

Phosphorous pentachloride (3.61 g) was added to a solution of the iodopyrimidone (321b; 5.30 g) in phosphorous oxychloride (18 ml). The mixture was refluxed for 3 h and the volatiles were removed under reduced pressure. Ice followed by methylene chloride were added to the residue. The organic phase was separated, washed with water and dried (MgSO4). The solvent was removed under reduced pressure to provide the chloride (321c; 4.96 g) as a light-brown sold, which was used without purification.

A mixture of MCPBA (1.46 g of 77% pure material) and the sulfide (321c; 1.0 g) in dichloromethane (15 ml) was



321a 321b 321c 321d 321e 321f 321

stirred at 0 C for 30 min and allowed to warm to room temperature overnight. The reaction mixture was filtered and the filtrate washed with 10% aq. potassium carbonate, dried (MgSO4) and concentrated under reduced pressure to give the desired sulfone (321d; 0.89 g) as a white solid.

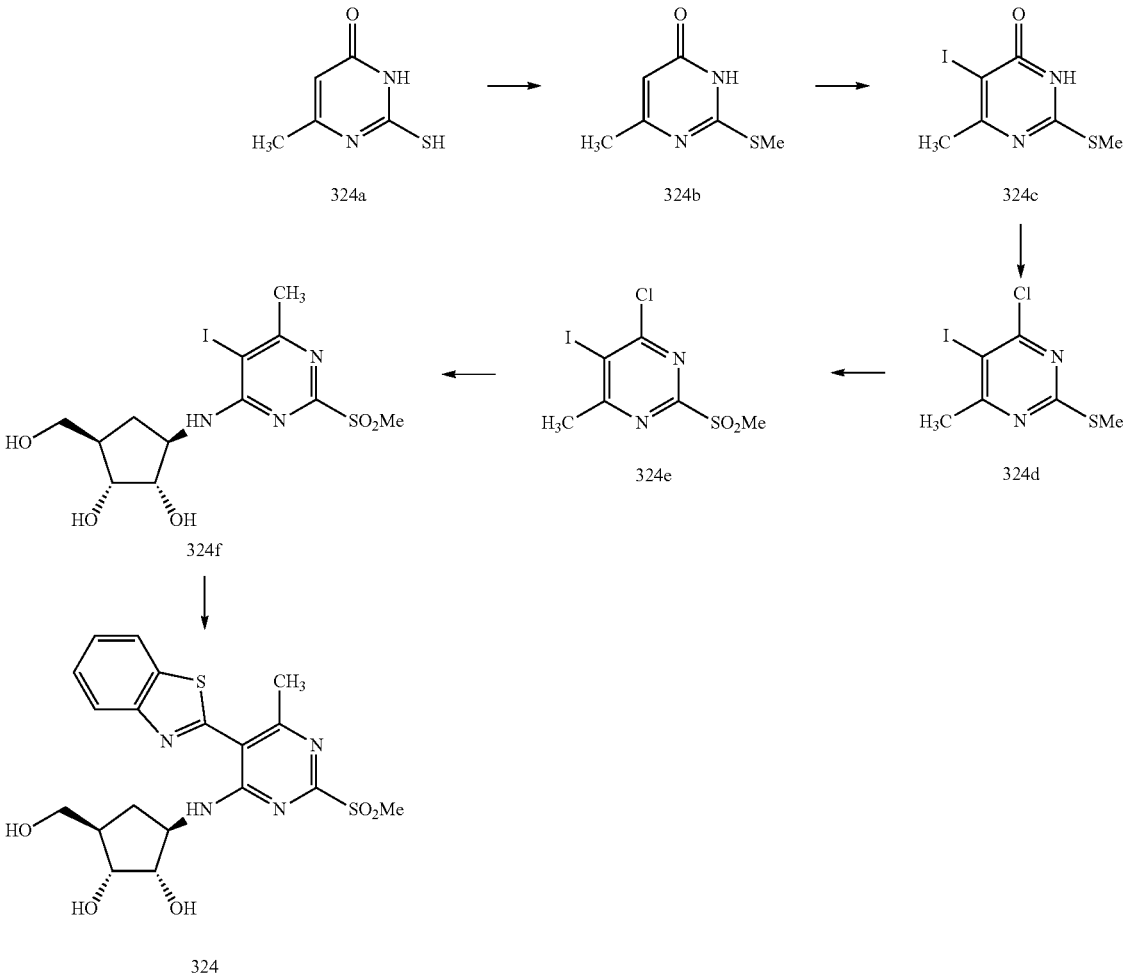
Amylamine (0.54 ml; 2 eq.) was added dropwise to a stirred solution of the sulfone (321d; 0.89 g) in anhydrous DMF (10 ml), under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature, overnight. The reaction was partitioned between EtOAc and water. The organic phase was separated, washed with water (×3), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield the 2-aminopyrimidine (321e; 0.181 g).

A mixture of the pyrimidine (321e; 0.1 g), carbasugar (2a; 0.047 g) and triethylamine (0.18 ml) in ethanol (5 ml) was refluxed overnight. After cooling, the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methylene chloride:methanol (20:1) as eluent to give the desired product (321f; 0.055 g).

A mixture of tri-n-butylstannyl benzothiazole (186 mg), iodide (321f; 55 mg), dichlorobis(triphenylphosphine)palladium(II) (30 mg), copper(I) Iodide (16 mg) and triethylamine (0.12 ml) in dioxane (3 ml) was heated to 100 C for 10 h. After cooling the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methylene chloride:methanol (20:1) as eluent to give the desired product (321; 11 mgs). A considerable amount of impure product was also obtained but was not pursued at this time.

Example 324

Procedure T



324a 324b 324c 324d 324e 324f 324

To a solution of the pyrimidine (324a; 522.3 g) in DMSO (5 L), potassium carbonate (535.6 g) followed by iodomethane (245 ml) were added while maintaining a reaction temperature of 22-25 C (dry ice/acetone bath). When the addition was complete the reaction was allowed to stir at room temperature overnight. Ice (7 L) and water (13 L) were added to the reaction. After 0.5 h., the mixture was filtered and the solid washed with cold water, cold acetonitrile and cold ether to give the methyl sulfide (324b; 95.7 g).

To the filtrate was added 50% aq. HCl (300 ml) while cooled in a dry ice/acetone bath. After stirring for 5 min, the white solid was collected, After washing with cold water, acetonitrile and ether a further portion of the methylsulfide (324b; 361.2 g) was recovered.

A mixture of the pyrimidone (324b; 437 g), iodine (852.6 g) and sodium hydroxide (134.2 g) in water (2 L) was heated to 80 C for 15 h. After cooling the reaction was neutralized with acetic acid and the solid collected to give the iodide (324c; 656 g) as a light-brown solid. Used in the next step without purification.

The iodide (324c; 500 g) was added to phosphorous oxychloride (1 L) and heated to reflux for 1 h. After cooling, the volatiles were removed under reduced pressure. The resulting solid was portioned between chloroform and ice. Potassium carbonate was added (to pH=7-8). The aqueous layer was further extracted with chloroform (total 8 L). The combined organic phases were washed with 2 L of 1N NaOH. The organic phase was dried (MgSO4) and concentrated to give the chloride (324d; 470 g) as a yellow solid.

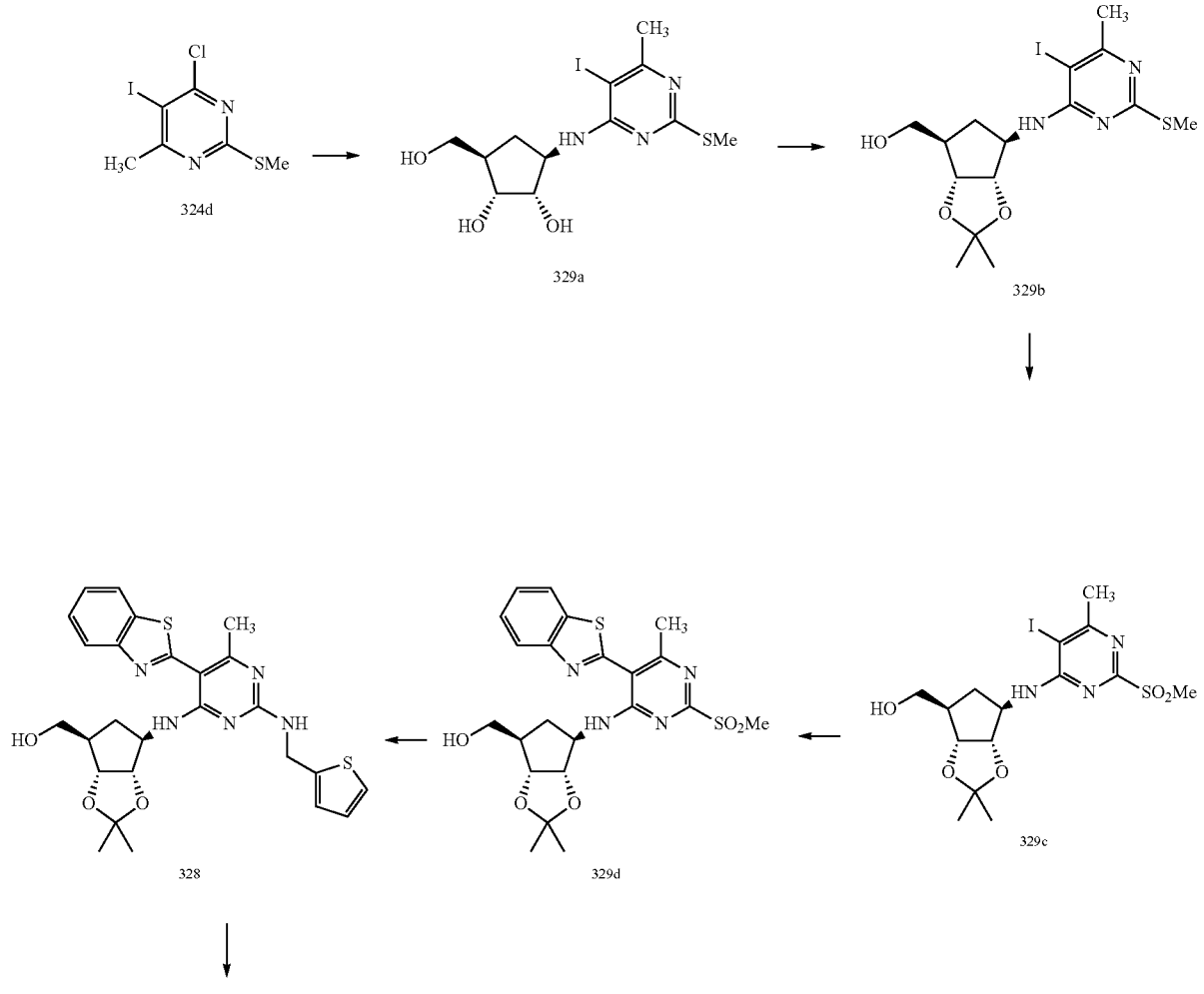
To the sulfide (324d; 2.00 g) in dichloromethane (50 ml) was added MCPBA (3.50 g of 77% pure material) while cooled in an ice bath and the resulting reaction was allowed to warm to room temperature overnight. The reaction was filtered and the filtrate was washed with 10% aq. NaOH. The organic phase was separated, dried (MgSO4), and concentrated under reduced pressure to give the desired sulfone (324e; 2.06 g) as a white solid. Used without purification.

A mixture of the sulfone (324e; 1.213 g), the carbasugar (2a; 0.736 g) and triethylamine (1.12 ml) in acetonitrile (25 ml) was heated to 60 C for 4 h, under an atmosphere of nitrogen. After cooling, the volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using dichloromethane; methanol (10:1) as eluent. Gave the desired adduct (324f; 0.968 g).

A mixture of tri-n-butylstannyl benzothiazole (191 mg), iodide (324f; 100 mg), dichlorobis(triphenylphosphine)palladium(II) (32 mg), copper(I) Iodide (17 mg) and triethylamine (0.125 ml) in dioxane (3 ml) was heated to 100 C for 2 h. After cooling the reaction was filtered through a pad of celite and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using methylene chloride:methanol (10:1) as eluent to give the desired product (324; 17.6 mgs). A considerable amount of impure product was also obtained but was not pursued at this time.

Example 328 and 329

Procedure U



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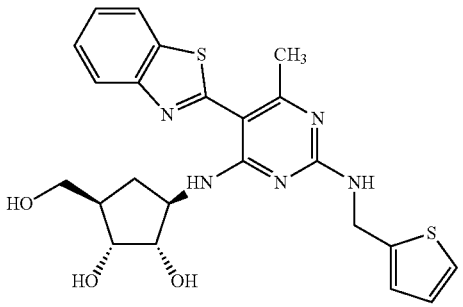


329; HCl salt

Triethylamine (111.0 g) was added to a mixture of the pyrimidine (324d; 72.3 g) and carbasugar (2a; 40.0 g) and the resulting reaction heated to 70 C, overnight. After cooling, the volatiles were removed under reduced pressure to give the crude adduct (329a; used without purification).

To the crude triol (329a; above) was added acetone (2 L) followed by 2,2-dimethoxypropane (55 ml) and methanesulfonic acid (15 ml) while cooled in an ice bath. When the addition was complete the reaction was allowed to warm to room temperature overnight. The reaction mixture was partitioned between EtOAc (4 L), water (1 L) and brine (200 ml). The organic phase was separated, washed with brine, dried (MgSO4) and concentrated. The residue was purified by column chromatography to give the desired primary alcohol (329b; 78.2 g) as a yellow solid.

MCPBA (1.096 g of 77% pure material) was added to a dichloromethane (15 ml) solution of the sulfide (329b; 0.932 g) while cooled in an ice bath, under an atmosphere of nitrogen. The resulting mixture was allowed to warm to room temperature overnight. The suspension was filtered and the filtrate washed with 10% aq. sodium thiosulfate followed by 10% aq. potassium carbonate, dried (MgSO4) and concentrated under reduced pressure to give the desired sulfone (329c; 0.698 g) as a white solid. This material was used without purification.

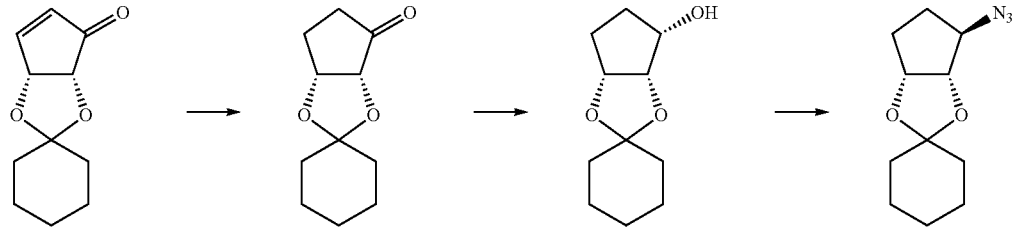
A mixture of tri-n-butylstannyl benzothiazole (1.23 g), iodide (329c; 698 mg), dichlorobis(triphenylphosphine)palladium(II) (197 mg), copper(I) Iodide (98 mg) and triethylamine (0.763 ml) in dioxane (20 ml) was heated to 100 C for 1 h. After cooling the reaction was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The filtrate was washed with 10% aq. HCl, water, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using methylene chloride:methanol (97:3) as eluent to give the desired product (329d; 422 mgs), as a light-brown solid.

2-Thiophenemethylamine (0.042 ml) was added dropwise to a solution of the sulfone (329d; 0.100 g) in acetonitrile (3 ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen, overnight. After cooling, the reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried (MgSO4) and concentrated under reduced pressure. Upon concentration the 2-aminopyrimidine (328; 0.042 g) was collected as a yellow solid. A considerable amount of product remained in the filtrate but was not pursued at this time. In most examples the desired product was purified and obtained via silica gel column chromatography.

1N aq. HCl (5 ml) was added dropwise to a solution of the dimethyl acetal (328; 36 mg) in dioxane (5 ml) and water (5 ml) and the resulting mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the solid washed with diethyl ether. Gave the desired triol (329; 27.6 mgs), as the hydrochloride salt, a light-brown solid.

Example 332 and 327

Procedure V



327a 327b 327c 327d

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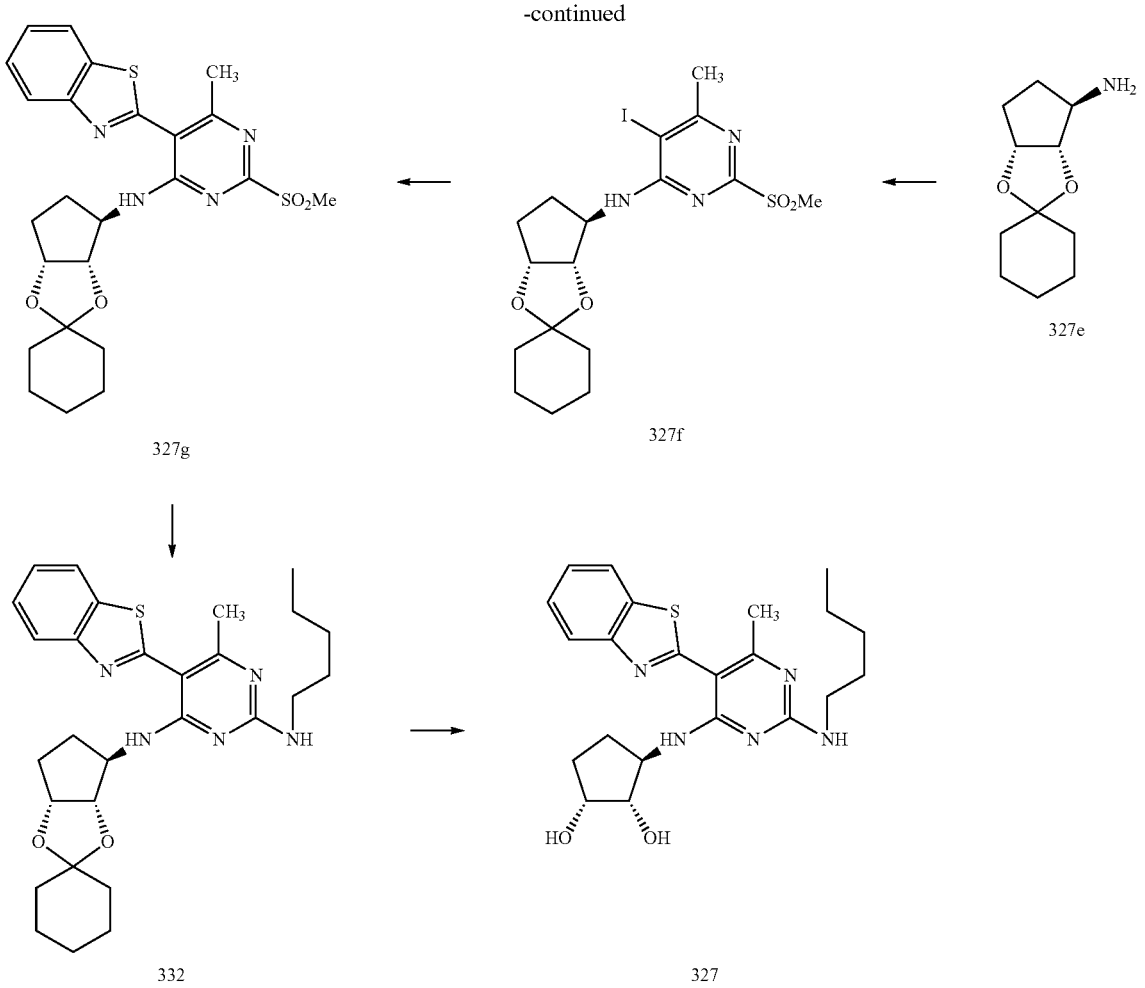


10% Pd/C (0.5 g) was added to a solution of the enone (327a; 1.0 g; prepared according to the procedures set forth in Helvetica Chimica Acta 1982, vol 65, page 2570 and patent U.S. Pat. No. 4,859,677) in ethanol (10 ml) and the resulting suspension was placed under an atmosphere of hydrogen overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with ethanol. The filtrate was concentrated under reduced pressure to give the ketone (327b; 0.98 g), used without purification.

Sodium borohydride (0.281 g) was added to a stiffed solution of the ketone (327b; 0.98 g) in methanol (50 ml) while cooled in an ice bath. The resulting mixture was stirred for 1 h. and water was added. Most of the methanol was removed under reduced pressure and the remaining residue extracted with dichloromethane (×3). The combined organic phases were dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography to yield the alcohol (327c; 0.895 g), as a colourless oil.

To a solution of the alcohol (327c; 0.895 g) in dichloromethane (25 ml) was added triethylamine (0.945 ml) followed by methanesulfonyl chloride (0.42 ml) and the resulting mixture stiffed for 2 h. The reaction was partitioned between dichloromethane and dil. aq. HCl. The organic phase was separated, washed with water, dried (MgSO4) and concentrated to give the crude, intermediate, mesylate. The mesylate was dissolved in DMF (30 ml) and sodium azide (0.352 g) was added and the resulting mixture was heated to 100 C, under an atmosphere of nitrogen, overnight. After cooling, the reaction mixture was partitioned between EtOAc and water. The organic phase was separated, washed with water (×3), dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the desired azide (327d; 0.48 g). ^{1}H NMR ($CDCl_3$) δ 1.34-1.42 (m, 2H), 1.49-1.64 (m, 8H), 1.70-1.74 (m, 1H), 1.76-1.83 (m, 1H), 1.86-1.91 (s, 1H), 1.98-2.05 (m, 1H), 3.96 (d, 1H, J=4.6 Hz), 4.38 (dd, 1H, J=5.5 and 1.2 Hz) and 4.70 (app. t, 1H, J=5.3 Hz). 13C NMR (CDCl3)

δ 23.58, 23.99, 25.15, 27.65, 30.64, 33.28, 35.86, 66.69, 79.66, 83.97 and 110.90.

10% Pd/C (0.25 g) was added to a solution of the azide (327d; 0.48 g) in ethanol (5 ml) and the resulting suspension was placed under an atmosphere of hydrogen overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with ethanol. The filtrate was concentrated under reduced pressure to give the amine (327e; 0.98 g), used without purification.

A mixture of the sulfone (324e; 0.89 g), the amine (327e; 0.44 g) and triethylamine (1.56 ml) in acetonitrile (15 ml) was heated to reflux, under an atmosphere of nitrogen, overnight. After cooling, the reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue purified by silica gel

column chromatography using EtOAc; hexanes (3:10) as eluent. Gave the desired adduct (327f; 0.968 g).

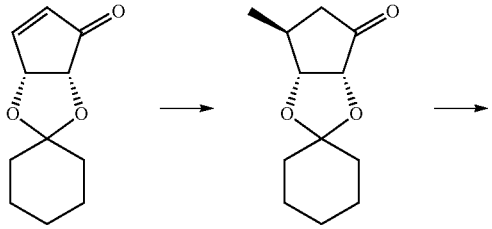
A mixture of tri-n-butylstannyl benzothiazole (0.816 g), iodide (327f; 475 mg), dichlorobis(triphenylphosphine)palladium(II) (137 mg), copper(I) Iodide (74 mg) and triethylamine (0.55 ml) in dioxane (15 ml) was heated to 100 C for 1 h. After cooling the reaction was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The filtrate was washed with 10% aq. HCl, water, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired product (327g), as a light-brown solid.

Amylamine (0.22 g) was added dropwise to a solution of the sulfone (327g; 0.25 g) in acetonitrile (5 ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen, overnight. After cooling, the reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried (MgSO4) and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to give the desired product (332; 0.196 g), as a white solid.

4N HCl in dioxane (5 ml) was added dropwise to a solution of the cyclohexyl acetal (332; 36 mg) in dioxane (3 ml) and water (5 ml) and the resulting mixture was stirred at room temperature for 2 h. The volatiles were removed under reduced pressure. To the residue was added methanol followed by triethylamine and the mixture concentrated to dryness. The residue was purified by silica gel column chromatography using dichloromethane:methanol (97:3) as eluent to give the desired diol (327; 0.106 g) as a white solid.

Example 335

Procedure W



327a 335a

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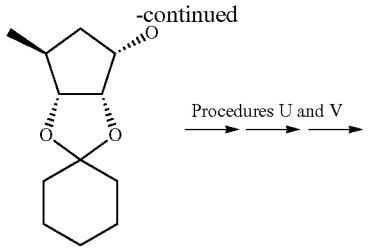
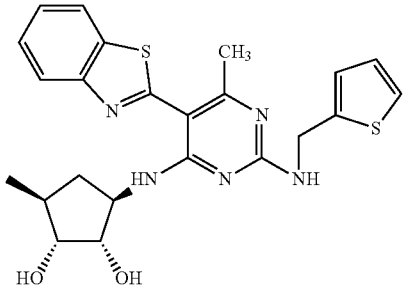


335b



335

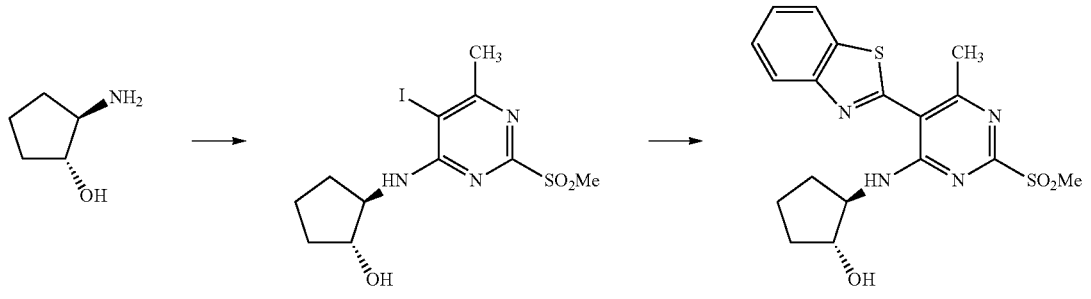
Using the procedure set forth in Journal of Medicinal Chemistry, 1992, vol 35, page 1787, 1.0 g of enone (327a) was transformed into the ketone (335a: 0.502 g).

Using the same reference 0.50 g of the ketone (335a) was converted into the alcohol (335b; 0.496 g).

Using the chemistries set forth in procedures U and V, alcohol (335b) was converted into diol (335).

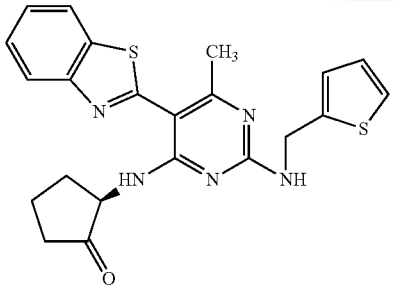
Example 333 and 338

Procedure X

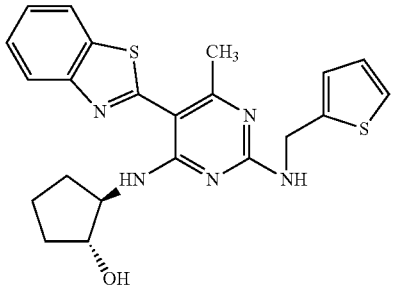


338a 338b 338c

-continued



338



333

A mixture of the sulfone (324e; 0.60 g), the racemic amine (338a; 0.2 g; Aldrich) and triethylamine (1.01 ml) in acetonitrile (15 ml) was heated to reflux, under an atmosphere of nitrogen, overnight. After cooling, the reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue purified by silica gel column chromatography using EtOAc; hexanes (1:1) as eluent. Gave the desired adduct (338b; 0.252 g), as a white solid.

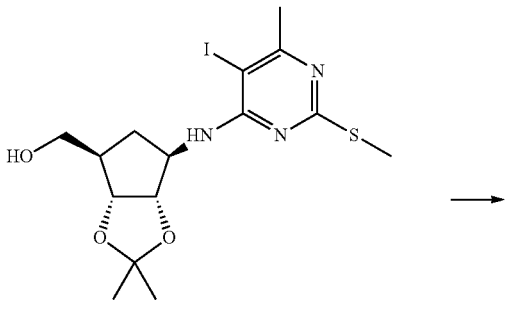
A mixture of tri-n-butylstannyl benzothiazole (0.538 g), iodide (338b; 252 mg), dichlorobis(triphenylphosphine)palladium(II) (91 mg), copper(I) Iodide (48 mg) and triethylamine (0.36 ml) in dioxane (10 ml) was heated to 100 C for 1 h. After cooling the reaction was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The filtrate was washed with 10% aq. HCl, water, dried (MgSO4) and the volatiles were removed under reduced pressure. EtOAc was added to the residue and the desired benzthiazole (338c; 0.152 g) was collected as a light-brown solid.

2-Thiophenemethylamine (0.19 ml) was added dropwise to a solution of the sulfone (338c; 0.150 g) in acetonitrile (12 ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen, overnight. After cooling, the reaction mixture was concentrated under reduced pressure from which the desired alcohol (333) was collected as a white solid. This solid was washed with water to give 0.154 g.

To the alcohol (333; 0.05 g) in dichloromethane (3 ml) was added the Dess-Martin periodinane (0.049 g) and the resulting mixture heated to 70 C for 6 h. A further portion of the periodinane (0.049 g) was added and heating was continued for a further 2 h. After cooling, the reaction mixture was partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried (MgSO4) and concentrated. The residue was purified by silica gel plate chromatography to give the ketone (338; 0.004 g), as a white solid.

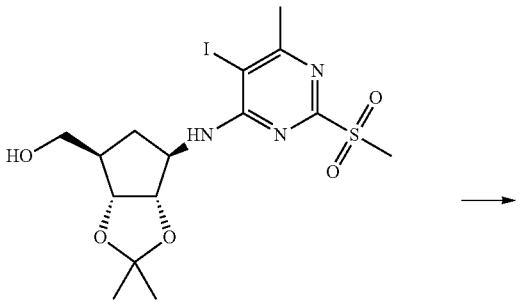
Example 524

Procedure Y

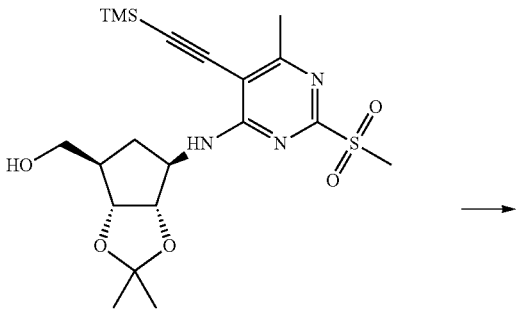


329b

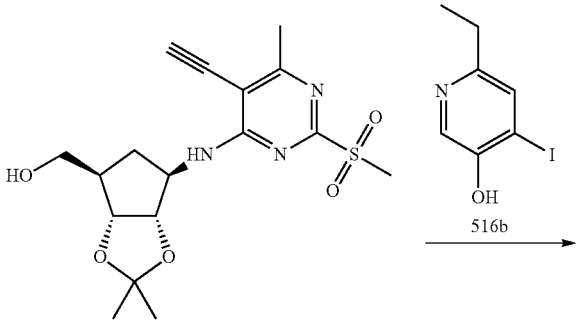
-continued



524a

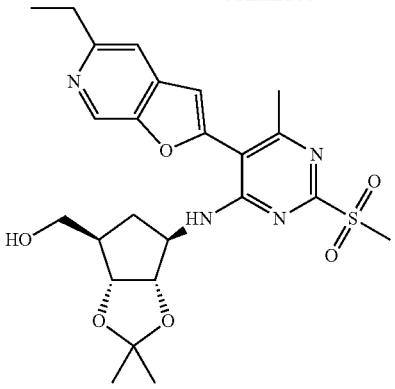


524b

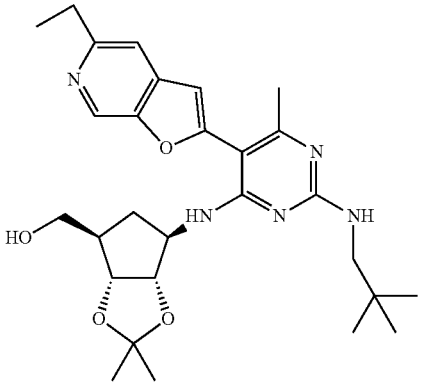


524c

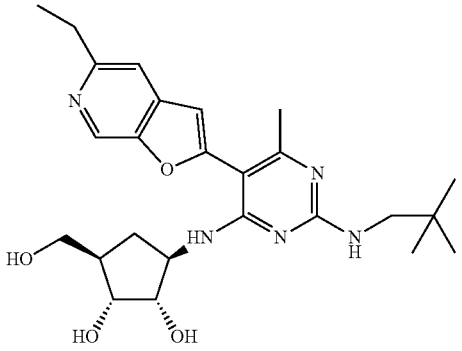
-continued



524d



524e



524

Step 1:

The starting iodide (329b, 500 mg, 1.1 mmol) was dissolved in methylene chloride (20 mL) and 77% m-CPBA (543 mg, 2.43 mmol) was added. The reaction was stirred at room temperature for 1 hour and then quenched with aqueous potassium carbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to provide the desired product (540 mg). [M+H]=484.13.

Step 2:

Compound 524a (540 mg, 1.1 mmol), TMS-acetylene (437 mg, 4.46 mmol), $Pd(PPh_3)_4$ (254 mg, 0.22 mmol), CuI (80 mg), triethylamine (0.61 mL, 4.4 mmol) were dissolved in dioxane and stirred at 60 C for 2 hours and room temperature overnight. The reaction was quenched with water and the product was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Column chromatography (1:1 Hexanes/ethyl acetate) provided the desired product (410 mg). [M+H]=454.34

Step 3:

Compound 524b (400 mg, 0.88 mmol) was dissolved in THF (15 mL) and cooled in an ice bath. Tetramethylammonium fluoride (50 mg) was added to the reaction and stirred for 2 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide the desired product that was used without further purification (290 mg). [M+H]=382.29

Step 4:

Compound 524c (250 mg, 0.65 mmol), compound 516b (163 mg, 0.65 mmol), $Pd(PPh_3)_4$ (150 mg), CuI (70 mg), and triethylamine (0.36 mL) were dissolved in dioxane and stirred at 80 C for 2 hours. The reaction was quenched with brine and extracted with ethyl acetate. The organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc 4.5% MeOH/EtOAc) to provide the desired product (200 mg). [M+H]=503.3

Step 5:

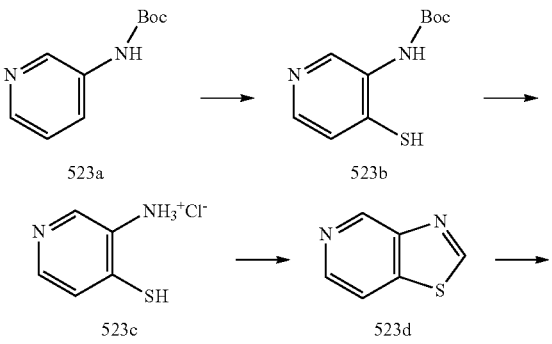
Compound 524d (50 mg, 0.099 mol) and neopentylamine (0.2 mL) were dissolved in acetonitrile (2 mL) and stirred in a pressure bottle at 80 C overnight. The reaction was cooled to room temperature and the solid were filtered to provide the desired product (50 mg). [M+H]=510.4

Step 6:

Compound 524e (50 mg, 0.093 mmol) was dissolved in a mixture of 4M HCl dioxane (1 mL), MeOH (3 mL) and water (0.2 mL). The reaction was stirred at room temperature for 2 hours and then all solvents were removed under reduced pressure. The residue was triturated with methylene chloride to provide the desired product (35 mg). [M+H]= 470.4 1H NMR (DMSO-d6) 0.9 (s, 9H), 1.0-1.1 (m, 1H), 1.2-1.3 (m, 3H), 1.9-2.0 (m, 1H), 2.0-2.2 (m, 1H), 2.4 (m, 3H), 3.0-3.2 (m, 2H), 3.2-3.4 (m, 4H), 3.6-3.8 (m, 2H), 4.4-4.5 (m, 2H), 7.4 (s, 1H), 8.0 (m, 1H), 8.15 (m, 1H), 8.2 (m, 1H) 9.3 (s, 1H).

Example 523

Procedure Z



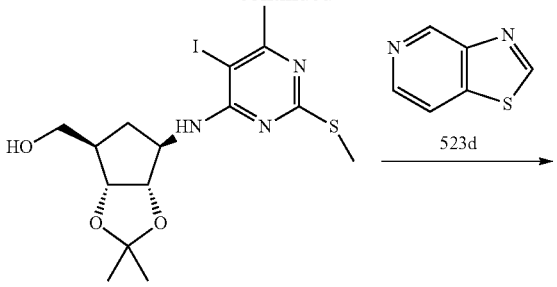
523a

523b

523c

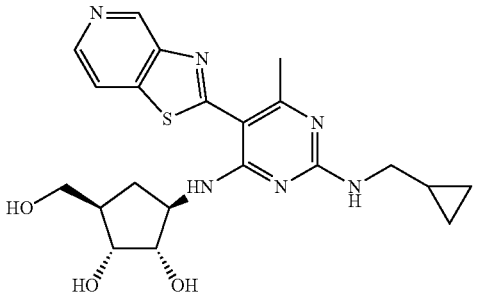
523d

-continued

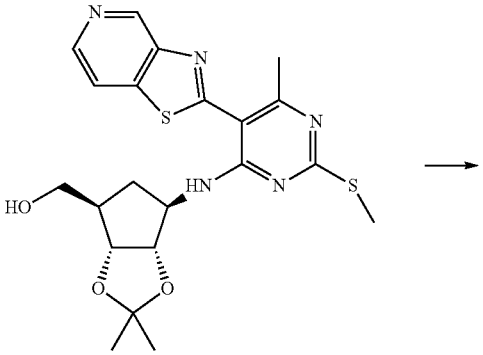


523d

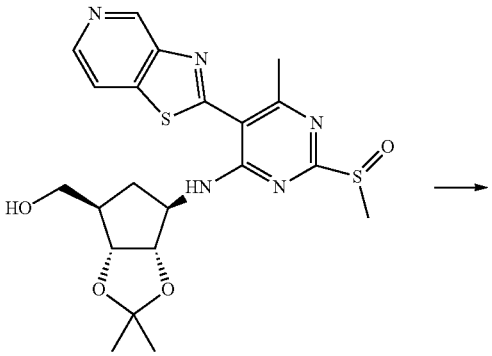
-continued



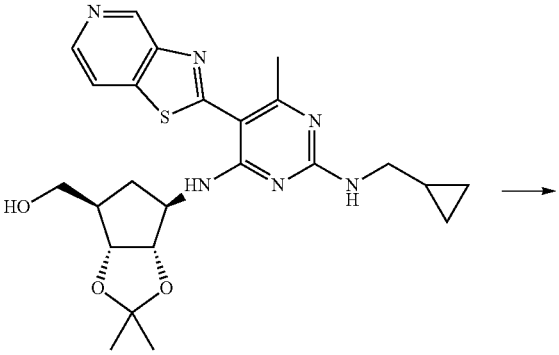
523



523e



523f



523g

Step 1:

The reaction to form 523b from 523a was performed in the same manner as U.S. Pat. No. 5,077,287, 31 Dec. 1991.

Step 2:

The reaction to form 523c from 523b was performed in the same manner as U.S. Pat. No. 5,077,287, 31 Dec. 1991.

Step 3:

Compound 523c (1.42 g, 8.8 mmol) was dissolved in formic acid (15 mL) and refluxed overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and 1N NaOH solution. The aqueous layer was extracted with ethyl acetate several times. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide the desired product (1.0 g) that was used without further purification. [M+H]=137.25.

Step 4:

See procedure F (Step 2) for the experimental conditions for the synthesis of 523e.

Step 5:

Compound 523e (75 mg, 0.163 mmol) was dissolved in methylene chloride (6 mL) and cooled in an ice bath. 77% m-CPBA (55 mg, 0.244 mmol) was added and the reaction was stiffed for 1 hour at the same temperature and then quenched with aqueous potassium carbonate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to provide the desired product (75 mg). [M+H]=476.2

Step 6:

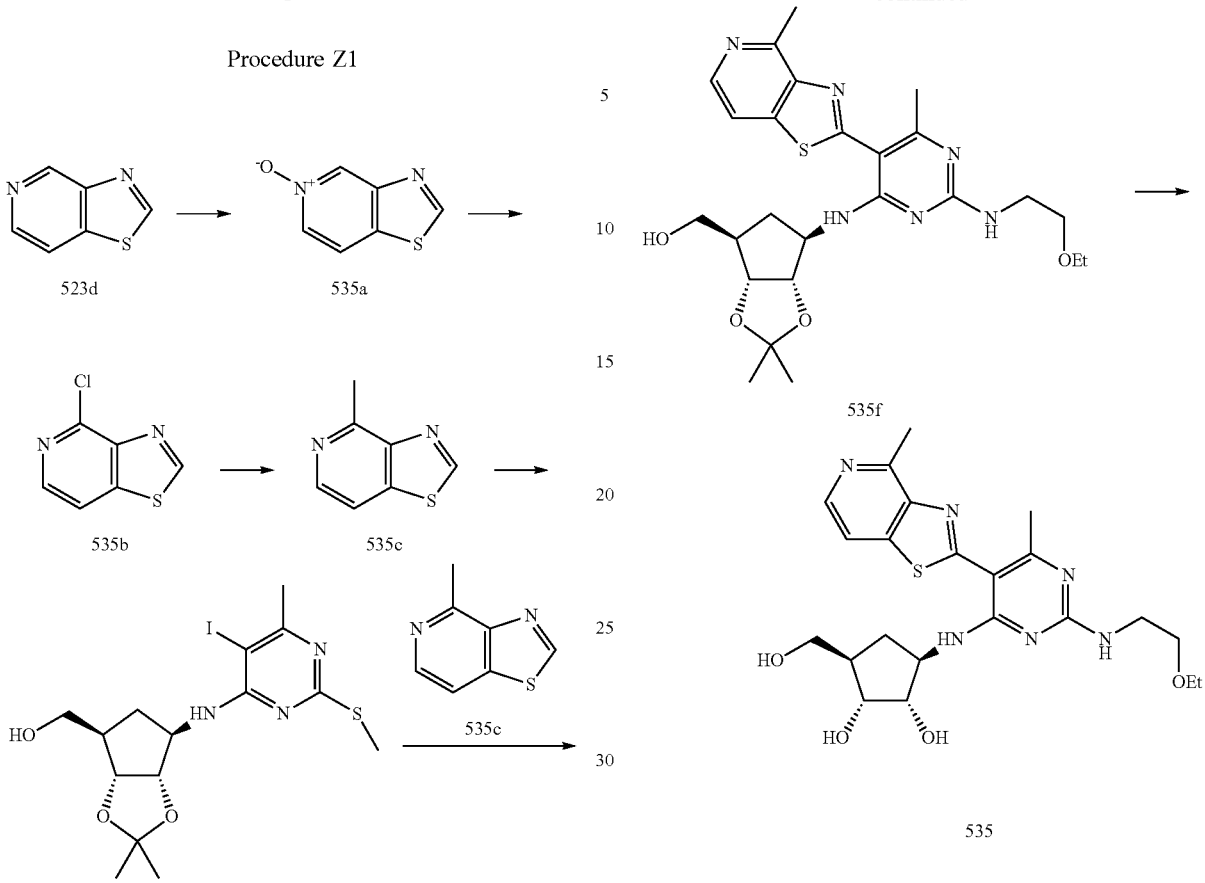
Compound 523f (75 mg, 0.15 mmol) was dissolved in acetonitrile (2 mL) and cyclopropylamine (0.1 mL) was added. The reaction was stirred at 80 C for 1 hour and then cooled to room temperature. The solids were filtered to provide the desired product (55 mg). [M+H]=483.2

Step 7:

Compound 523g (53 mg, 0.109 mmol) was dissolved in a mixture of 4 M HCl dioxane (1 mL), MeOH (3 mL) and water (0.1 mL) and stirred at room temperature for 2 hours. The solvents were removed and the residue was triturated with diethyl ether to provide the desired product (46 mg). [M+H]=443.2

Example 535

Procedure Z1



-continued

Step 1:

Compound 523d (670 mg, 4.9 mmol) was dissolved in methylene chloride (20 mL) and m-CPBA (1.65 g, 7.38 mmol) was added. The reaction was stiffed for 2 hours and then quenched with a solution of 1M potassium carbonate. The organic layer was dried over sodium sulfate and concentrated to provide compound 535a (450 mg). [M+H]=153.2

Step 2:

Compound 535a (400 mg, 2.61 mmol) was dissolved in phosphorus oxychloride (5 mL) and refluxed for 2 hours. The reaction was concentrated under reduced pressure and then quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide the desired product (180 mg). [M+H]=171.1

Step 3:

Compound 535b (180 mg, 1.05 mmol), methylboronic acid (200 mg), $Pd(PPh_3)_4$ (100 mg), and potassium carbonate (500 mg) were dissolved in dioxane (10 mL) and water (3 mL) and stirred at reflux for 4 hours. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (2:1 ethyl acetate/hexanes) provided the desired product (70 mg). [M+H]=151.1

Step 4:

Reaction was performed in the same manner as procedure F (Step 2). [M+H]=474.4

Step 5:

Reaction was performed in the same manner as procedure U (Step 5). [M+H]=490.3

Step 6:

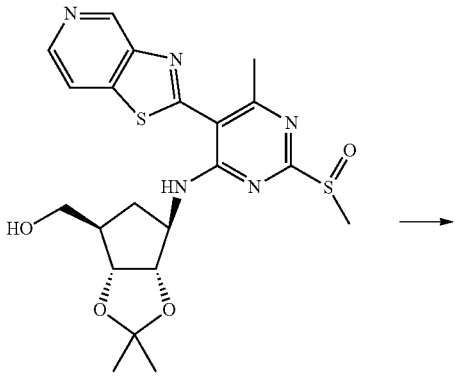
Reaction was performed in the same manner as procedure U (Step 6). [M+H]=515.5

Step 7:

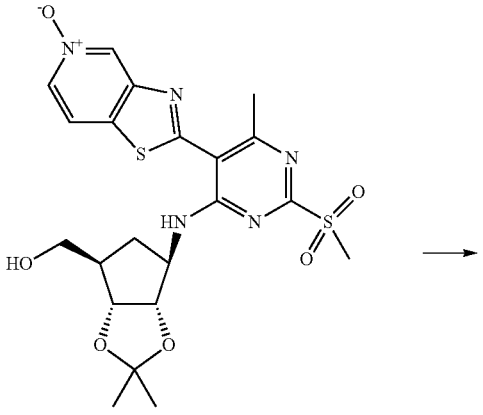
Reaction was performed in the same manner as procedure U (Step 7). [M+H]=475.2

Example 542

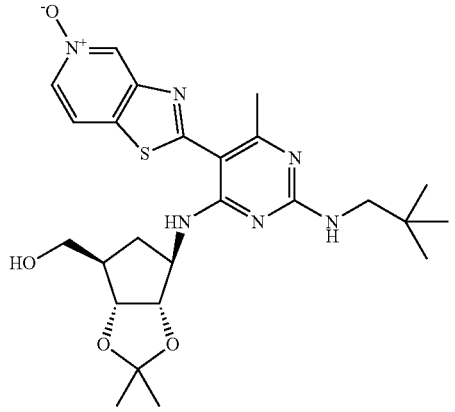
Procedure Z2



523f

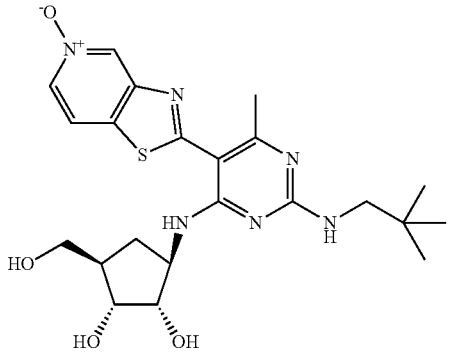


542a



542b

-continued



542

Step 1:

Compound 523f (100 mg, 0.21 mmol), m-CPBA (100 mg), and potassium carbonate (100 mg) were dissolved in methylene chloride (5 mL) and stirred at room temperature for 2 hours. The reaction was quenched with water and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide the desired product (100 mg).

Step 2:

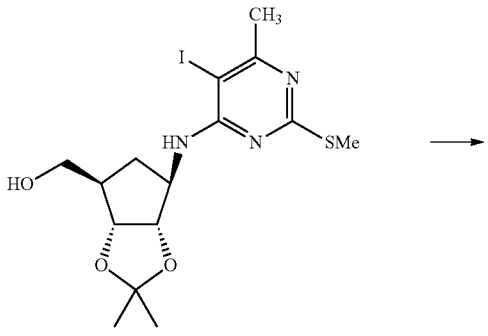
Compound 542a (100 mg, 0.2 mmol) and neopentylamine (0.2 mL) were dissolved in acetonitrile (2 mL) and stiffed at 100 C for 3 hours. The solvent was removed under reduced pressure and the solids were triturated with diethyl ether to provide the desired product (30 mg)

Step 3:

Reaction was performed in the same manner as procedure U (Step 7). [M+H]=475.4

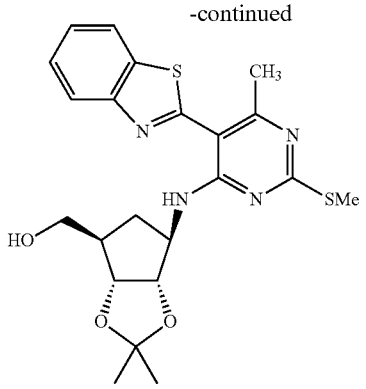
Examples 248 and 252

Procedure Z3

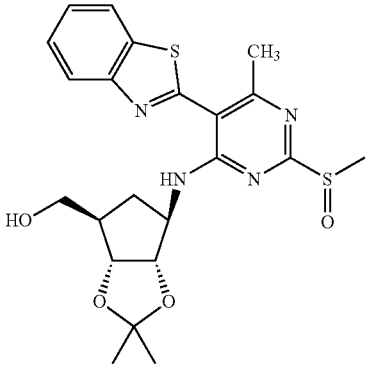


329b

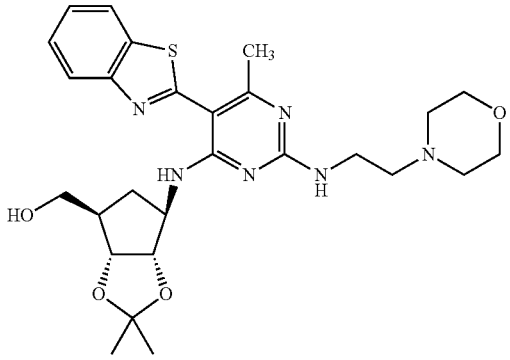
-continued



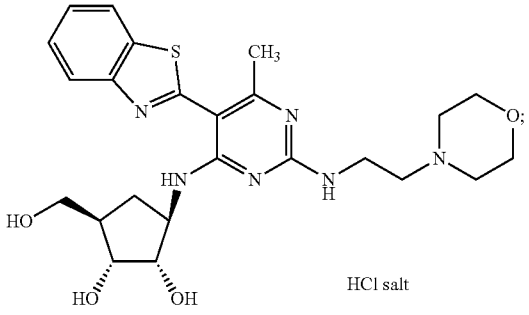
252a



252b



248



HCl salt

252

Step 1:

Compound 329b was converted to 252a using procedure U, step 4 (conversion of 329b to 329c)

Step 2:

Compound 252a was converted to 252b using Procedure Z, step 5.

Step 3:

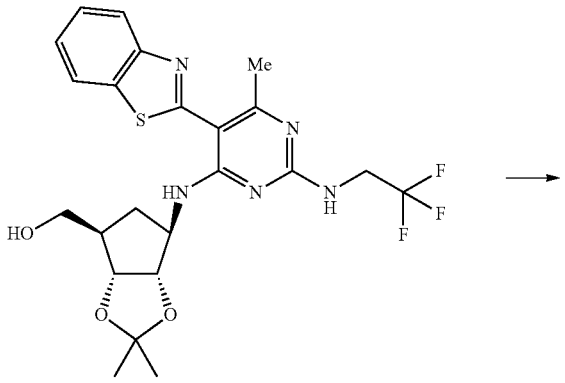
Compound 252b was converted to 248 using Procedure Z, step 6 (longer reaction time, 4-16 hrs)

Step 4:

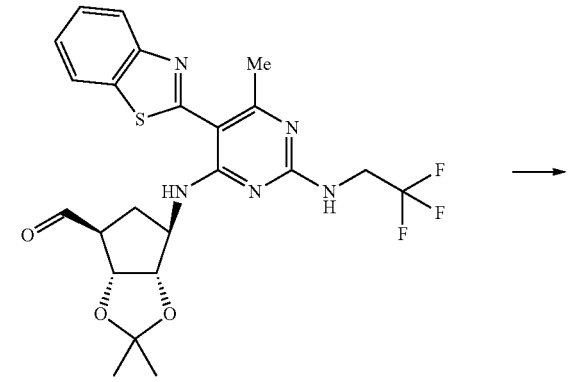
Compound 248 was converted to 252 using Procedure Z, step 7 (longer reaction time, 4-16 hrs).

Example 1015

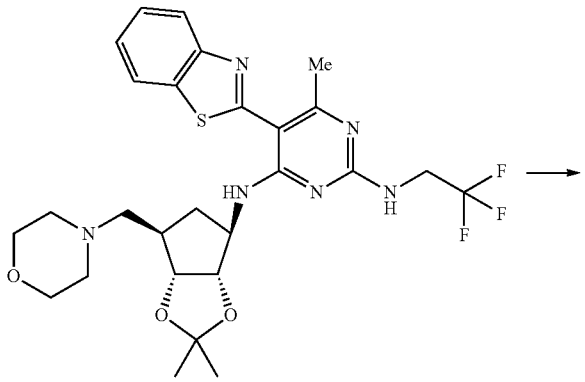
Procedure Z10



1015a



1015b



1015c

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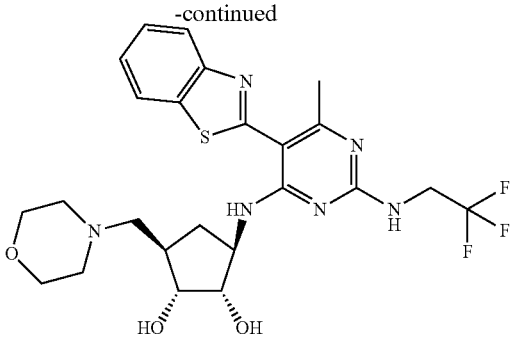


1015

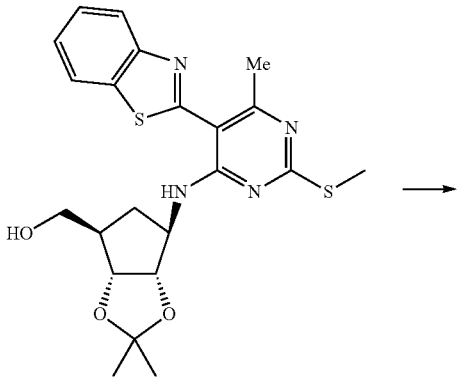
To the SM, 1015a (prepared as in procedure U, 1 g, 2.0 mmol) in CH_2Cl_2/THF (50/25 ml) at 0° was added Dess-Martins periodinane (1.27 g, 3.0 mmol). 0°-10° C., 2 hrs. TLC (50/50 EtOAc/hexanes) indicated product and SM. So added more oxidant (~650 mg) and kept at that temp for additional 2 hrs. Then stored in the refrigerator (<5° C.), overnight. Then quenched with 10% sodium thiosulfate solution (50 ml)/satd bicarbonate (50 ml). Diluted with CH_2Cl_2 (100 ml). Stirred vigorously for 5 min. The org layer was separated and washed with 10% sodium thiosulfate solution (50 ml)/satd bicarbonate (50 ml), brine (100 ml), dried (Na2SO4), filtered and concentrated. The crude material was purified by flash silica chromatography using 0/100 to 60/40 of EtOAc/hexanes to give 1015b, wt=740 mg (white solid).

To 1015b (140 mg, 0.276 mmol) in dichloroethane (5 ml) at room temperature was added morpholine (0.025 ml, 0.276 mmol) and sodium triacetoxy borohydride (77 mg, 0.359 mmol). Stirred at room temp for 1.5 hr. TLC (5/95 MeOH/CH_2Cl_2) indicated reaction completion. Cooled reaction mixture in an ice bath, and quenched with addition of satd NaHCO3, dropwise. Diluted with CH2Cl2 (50 ml), washed with satd NaHCO3 solution (50 ml), dried (Na2SO4), filtered and concentrated. The crude material was purified by flash silica chromatography using 0/100 to 5/95 of MeOH/CH_2Cl_2 to give 1015c, wt=83 mg.

1015c was converted to product 1015 using procedures described earlier (Z3, last step).

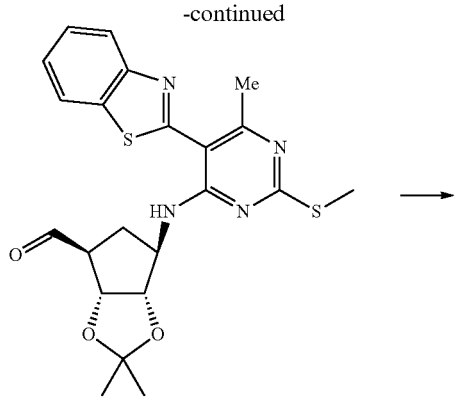
Example 1019

Procedure Z11

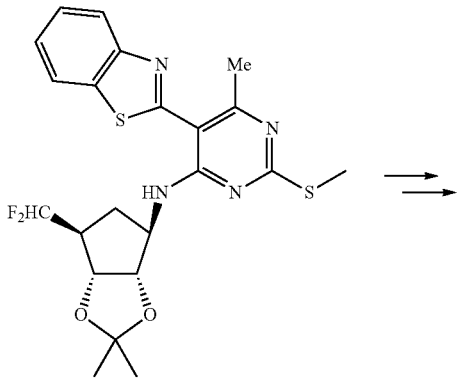


252a

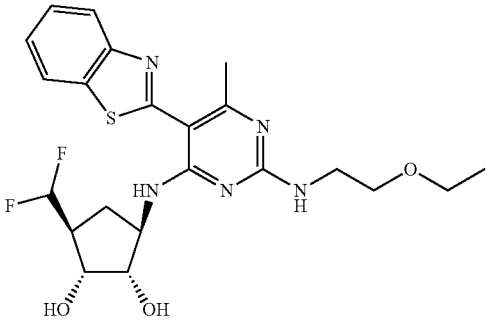
-continued



1019a



1019b



1019

To the 252a (100 mg, 0.22 mmol) in CH_2Cl_2 (5 ml) at 0° was added DM periodinane (112 mg, 0.26 mmol, 1.2 equiv). 0°-10° C., 1 hr. TLC (50/50 EtOAc/hexanes) showed reaction completion. Quenched with 10% sodium thiosulfate solution (25 ml)/satd bicarbonate (25 ml). Diluted with EtOAc (50 ml). Stirred vigorously for 5 min. The org layer was separated and washed with 10% sodium thiosulfate solution (25 ml)/satd bicarbonate (25 ml), brine (50 ml), dried (Na2SO4), filtered and concentrated. The crude material was purified by flash silica chromatography using 0/100 to 60/40 of EtOAc/hexanes to give 1019a, wt=81 mg (white solid).

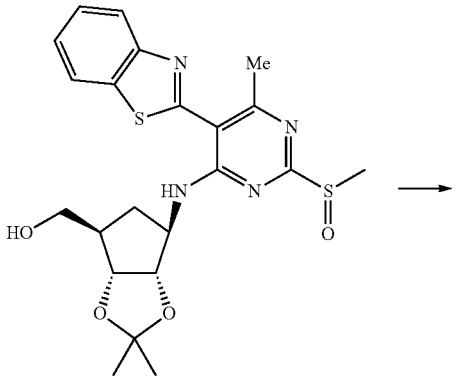
To the aldehyde, 1019a (81 mg, 0.18 mmol) in CH_2Cl_2 (3 ml) at RT was added Deoxo-Fluor, Bis(2-methoxyethyl) aminosulfur trifluoride (50% in THF, 1 ml). Maintained at room temp for 1 hr to two days (till reaction completion by TLC). Then quenched by pouring (DROPWISE) into ice cold satd NaHCO3, with vigorous stirring (~25 ml). Added CH_2Cl_2 (25 ml) and stirred for 10 min. Then poured into sep funnel, and separated the org layer. Extracted the aq layer

with CH_2Cl_2 (25 ml). The combined org layer was dried (Na2SO4), filtered and concentrated. The crude material was purified by flash silica chromatography using 0/100 to 50/50 of EtOAc/hexanes to give 1019b, wt=31 mg (white solid).

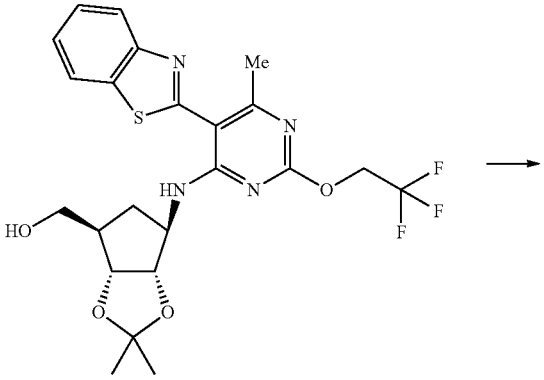
1019b was converted to product 1019 using procedures described earlier (Z3).

Example 1057

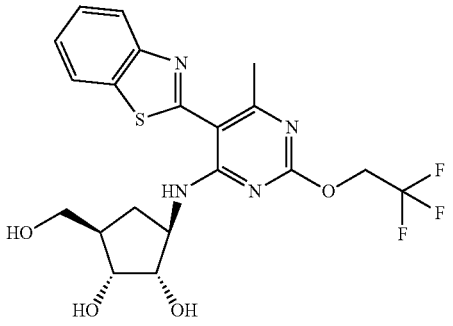
Procedure Z13



252b



1057a



1057

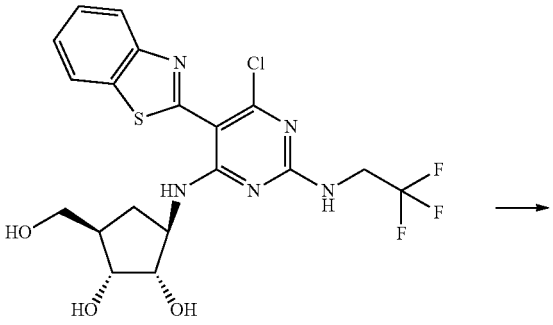
To a solution of trifluoroethanol (0.03 ml) in dry THF (3 ml) was added sodium hydride (60% dispersion in oil, 16 mg). Stirred at room temp for 15 min. Then added a solution of 252b (200 mg) in dry THF (3 ml). Heated to 100° C. and monitored by TLC till completion of reaction. Reaction was quenched by addition of saturated NH4Cl solution. Extracted organics into EtoAc (50 ml), washed with water (50 ml), brine (50 ml), dried (Na2SO4), filtered and concentrated. The crude material was purified by flash silica chromatography using EtOAc/hexanes to give 1057a.

1057a was converted to product 1057 using procedures described earlier (Z3, last step).

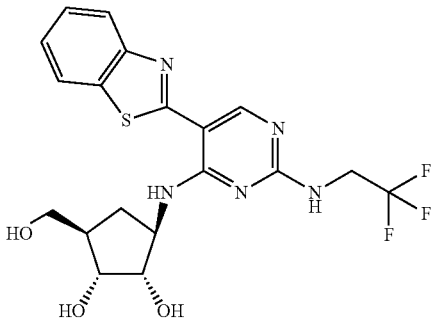
(Note: Rxn had to be heated to 45° C. for complete deprotection).

Example 1058

Procedure Z14



124

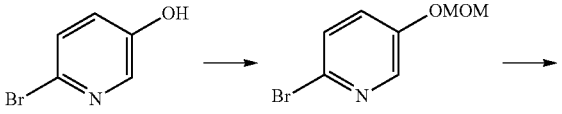


1058

Compound 124 (100 mg) was taken in gl AcOH (10 ml) and MeOH (10 ml). Added spatula tip of 20% $Pd(OH)_2/C$ (wet) and hydrogenated at ~40-50 psi of H2 using the Parr shaker, overnight. Then filtered thru celite, rinsed with MeOH and concentrated. The crude residue was purified by reverse phase HPLC, as described in Procedure C, to provide pure 1058.

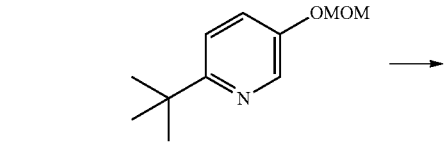
Example 1104

Procedure Z-15

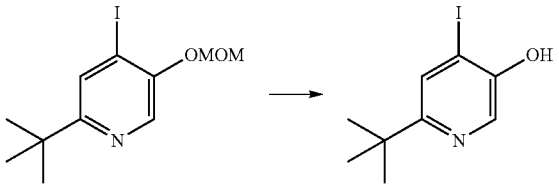


1104a 1104b

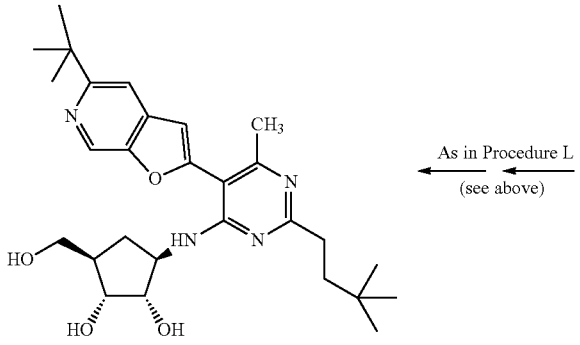
-continued



1104c



1104d 1104e



1104 (HCl salt)

Chloromethylmethyl ether (2.11 ml) in DMF (15 ml) was added to an ice bath cooled solution of the pyridol (1104a; 4.86 g; 28 mmol) in DMF (70 ml) under an atmosphere of nitrogen. The resulting mixture was allowed to attain room temperature overnight. Aqueous work-up and silica gel column chromatography gave the desired methoxymethyl ether (1104b; 3.86 g) as a pale-yellow oil. MH+, 218, 220.17

tert-Butylmagnesium chloride (Aldrich; 27.5 ml of a 2.0M solution in diethyl ether) was added to a stirred suspension of cuprous cyanide (1.232 g; 13.8 mmol) in anhydrous THF (60 ml) at −78 C, under an atmosphere of nitrogen. After 0.5 h., the bromide (1104b; 0.75 g; 3.4 mmol) in THF (2 ml) was added and after 2 h. at −78 C, the resulting reaction mixture was allowed to reach room temperature, overnight. sat. aq. sodium bicarbonate was added and the mixture was partitioned between EtOAc and water. The organic phase was separated, dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography on silica gel using EtOAc:hexanes (1:20) as eluent to give the desired alkylpyridine (1104c; 0.303 g) as a colourless oil. MH+, 196.25.

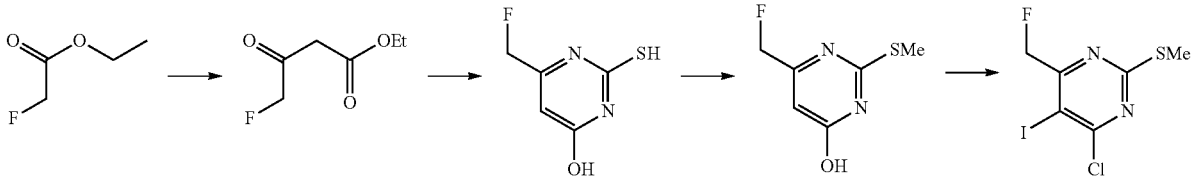
n-Butyl lithium (1.2 ml of a 1.6M solution in hexanes; Aldrich) was added dropwise to a stirred solution of the pyridine (1104c; 0.282 g; 1.46 mmol) in anhydrous THF (5 ml) at −78 C, under an atmosphere of nitrogen. after stirring for 1 h., iodine (0.441 g; 1.7 mmol) in THF (1 ml) was added and the temperature was maintained at −78 C for a further 2 h before the addition of sat. aq. NH4Cl. aqueous work-up and silica gel column chromatography using EtOAc-hexanes (1:10) gave the desired aryl iodide (1104d; 0.332 g) as a colourless oil. MH+, 322.17

TFA (1 ml) was added to a stirred solution of the ether (1104d; 0.320 g) in dichloromethane (4 ml) while cooled in an ice bath, under an atmosphere of nitrogen. When the addition was complete the reaction mixture was stirred at room temperature, overnight. The volatiles were removed under reduced pressure and the residue partitioned between EtOAc and sat. aq. sodium bicarbonate. The aqueous phase was separated and further extracted with EtOAc. The combined organic phases were dried (MgSO4) and concentrated to give the desired pyridol (1104e; 0.252 g) as a white solid. MH+, 278.17

Using the procedures set forth in procedure Y, 1104e was transformed into 1103 (MH+, 538.3) and 1104 (498.3)

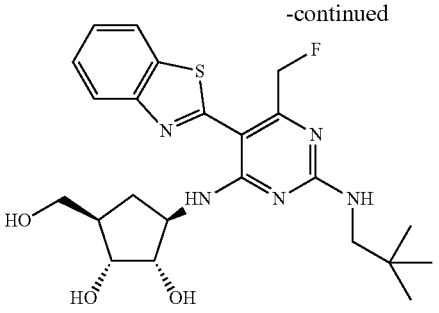
Example 1120

Procedure Z16



1120a 1120b 1120c 1120d

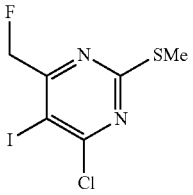
-continued



1120 (HCl salt)

As in Procedure U

(see above)



1120e

LDA (59 ml of a 2.0M solution in heptane/THF/ethylbenzene) was added to a solution of ethylacetate (9.7 ml; 109 mmol) in ether (100 ml) at −78 C under an atmosphere of nitrogen. After stirring for 0.5 h ethyl fluoroacetate (10.5 g; 99 mmol) was added and the resulting reaction mixture was allowed to reach room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. Aqueous work-up gave a residue that was purified by vacuum distillation to give the desired fluoroacetylacetate (1120a; 4.26 g), as a colourless oil.

A mixture of the fluoroacetylacetate (1120a; 4.24 g), thiourea (2.3 g) and 2M methanolic NaOMe (15 ml) were left to stand at room temperature for 48 h. The volatiles were removed under reduced pressure and the residue was dissolved in water. Acetic acid was added and the mixture was left at room temperature overnight. The desired pyrimidine (1120b; 1.26 g) was collected. a considerable amount of product remained in the mother liquor but was not pursued at this time.

Methyl iodide (0.398 g) was added dropwise to a stirred mixture of the pyrimidine (0.831 g) and potassium carbonate (0.870 g) while cooled in an ice bath. the resulting reaction mixture was allowed to reach room temperature overnight. water (40 ml) was added and the solid was collected (1120c; 0.262 g). A second crop precipitated but was set aside.

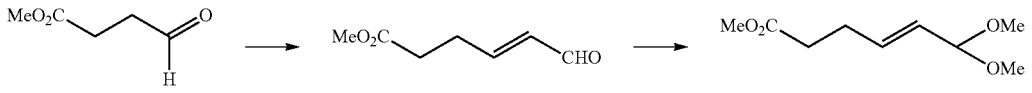
The methyl sulfide (1120c; 0.189 g), NIS (0.268 g) in acetonitrile was heated to reflux for 2.5 h. The volatiles were removed under reduced pressure and the residue partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with water, dried (MgSO4) and concentrated to give the pyrimidyl iodide (1120d) used without purification in the next step.

To the crude product (1120d) from the previous step was added phosphoryl chloride (2 ml) and the mixture was heated to reflux for 1 h. After cooling ice was added and the mixture partitioned between methylene chloride and water. The aqueous phase was made alkaline with the addition of potassium carbonate. The organic phase was separated, dried (MgSO4) and concentrated. Silica gel column chromatography using EtOAc:hexanes (1:20) gave the chloropyrimidine (1120e; 0.196 g). MH+, 319.6

Using chloropyrimidine (1120e) and the chemistry described in general method U or (procedure U), 1120 and 1121 were prepared.

Example 1132

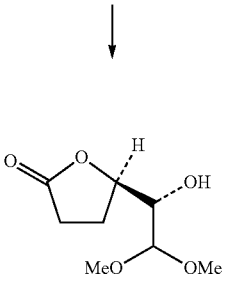
Procedure Z17



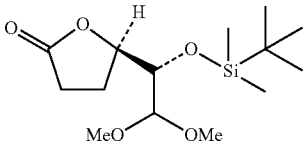
1132a

1132b

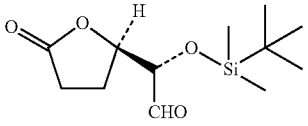
1132c



1132d

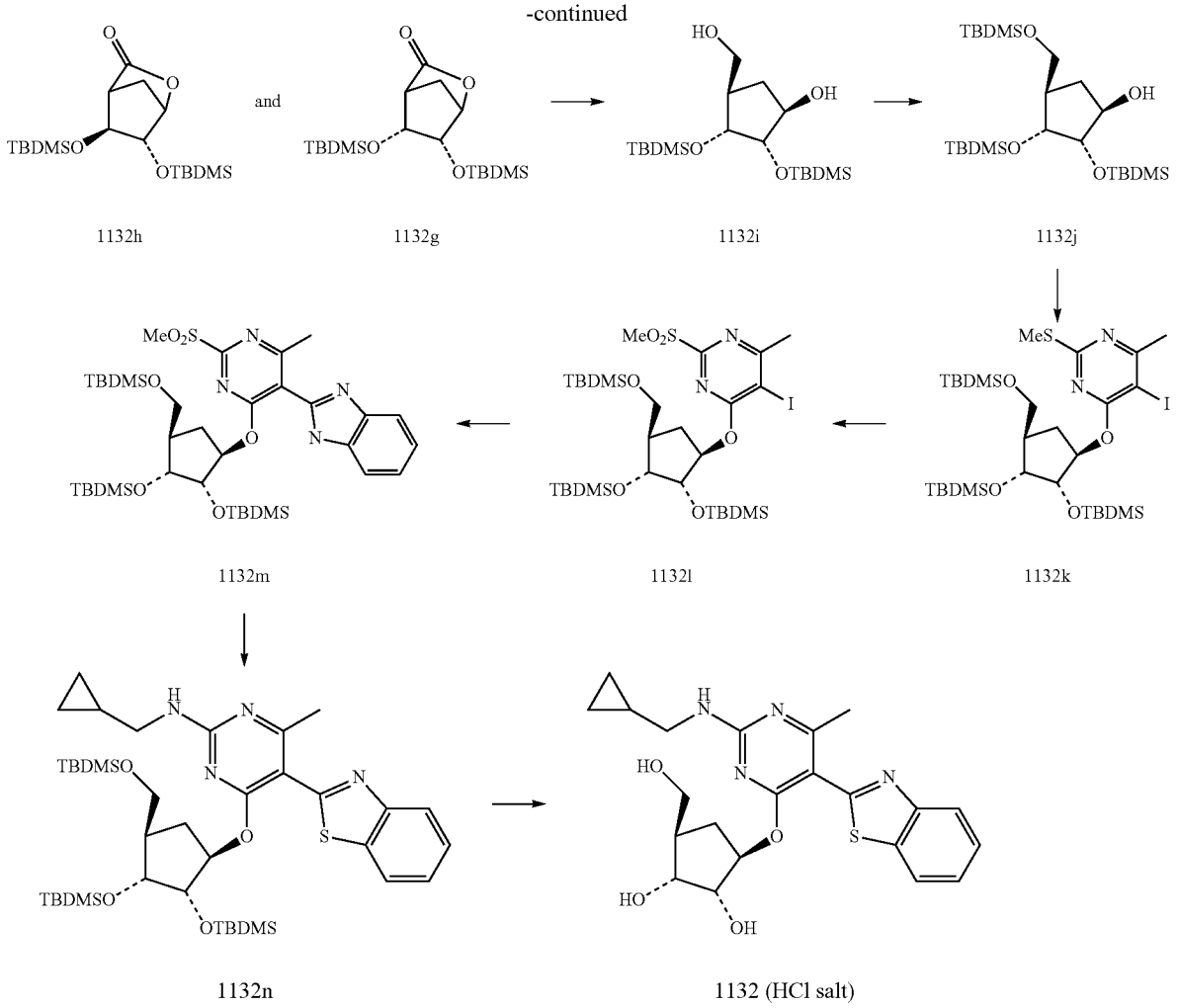


1132e



1132f

-continued



(Formylmethylene)triphenylphosphorane (8.26 g; 1.05 eq.) was added to a stirred solution of the aldehyde (1132a) at room temperature and the resulting mixture was stirred overnight. The volatiles were removed under reduced pressure and the residue was purified by silica gel column using EtOAc:hexanes; 1:5 as eluent to provide the desired unsaturated aldehyde (1132b; 2.11 g) as a yellow oil.

Ammonium nitrate (36 mgs) was added to a stirred solution of the aldehyde (1132b; 1.525 g) and trimethylorthoformate (1.368 g) in anhydrous methanol in an ice bath, under an atmosphere of nitrogen. The resulting mixture was allowed to warm to room temperature overnight, Sodium bicarbonate was added and the volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, washed with water, dried (MgSO4) and concentrated under reduced pressure to give the desired acetal (1132c; 1.976 g) as an orange oil, which was used without purification.

AD-mix—(6.30 g) was added to the dimethylacetal (1132c; 0.846 g) in tert-butanol (22.5 ml) and water (22.5 ml) followed by additional portions of $(DHQD)_2PHAL$ (31.5 mgs) and potassium osmate (31.5 mgs) and the resulting mixture stirred at room temperature for 3 h., before adding sodium sulfite (6.8 g). Aqueous work-up gave the crude lactone (1132d; 0.692 g), used without purification.

TBDMSOTf (1.54 ml) was added dropwise to a stirred solution of the alcohol (1132d; 1.167 g) and 2,6-lutidine (2.13 ml) in methylene chloride (15 ml) at room temperature, under an atmosphere of nitrogen. After 5 h., 5% aq. citric acid was added. Aqueous work-up and purification by silica gel column chromatography gave the desired silyl ether (1132e; 0.962 g) as a pale-yellow oil.

Lithium tetrafluoroborate (0.199 g) was added to the aqueous (2%) acetonitrile (18 ml) solution of the acetal (1132e; 0.585 g) and the resulting mixture was heated to 100 C (oil bath temp.) for 12 h. After cooling, sat. aq. sodium bicarbonate was added. Aqueous work-up gave the desired aldehyde (1132f; 0.376 g).

TBDMSOTf (0.243 ml) was added dropwise to a stirred solution diisopropylethylamine (0.184 ml) in dichloromethane (4 ml) at room temperature under an atmosphere of nitrogen. The mixture was stirred at room temperature for 10 min., before the addition of the aldehyde (1132f; 0.100 g) in dichloromethane (2 ml). The reaction was stirred overnight and sat. aq. ammonium chloride was added. The aqueous phase was separated and further extracted with methylene chloride. The combined organic phases were dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:50) to give the lactone (1132g; 0.033 g) followed by the isomer (1132h; 0.072 g). Both were obtained as colourless oils.

A THF solution of lithium tetraborohydride (0.7 ml Of a 2.0M) was added to a THF (3 ml) solution of the lactone (1132g; 0.100 g) while cooled in an ice bath, under an atmosphere of nitrogen and the resulting mixture was stirred at room temperature for a period of 6 h., before the addition of sat. aq. ammomium chloride. The mixture was partitioned between water and methylene chloride. The aqueous phase was separated and further extracted with methylene chloride (×2). The combined organic phases were dried (MgSO4) and concentrated to provide the diol (1132i; 0.071 g).

DMAP (0.062 g) was added to a stirred mixture of the diol (1132i; 0.062 g) and TBDMSCl (0.028 g) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was partitioned between methylene chloride and 10% aq. HCl. The organic phase was separated washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography to give the secondary alcohol (1132j; 0.052 g).

NaH (0.011 g of a 60% dispersion in mineral oil) followed by the pyrimidine (324d; 0.0425 g) were added to a THF solution of the alcohol (1132j; 0.046 g) at room temperature and the resulting mixture was stirred overnight. Additional portions of NaH (0.011 g) and pyrimidine (0.0425 g) were added and the reaction was stirred for a further 24 h. Sat. aq. ammonium chloride was added and the organics were extracted into methylene chloride, dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography using EtOAc:hexanes:1:99 to give the desired ether (1132k; 0.062 g), containing a small quantity of an impurity.

MCPBA (0.034 g of 77% pure material) was added to a stirred solution of the sulfide (1132k; 0.062) and sodium bicarbonate (0.069 g) in dichloromethane (3 ml) and the mixture was stirred at room temperature overnight. A further portion of MCPBA (0.034 g) and the mixture was stirred for a further 24 h. The reaction mixture was partitioned between EtOAc and 10% sodium thiosulfate. The organic phase was separated, washed with 10% aq. sodium carbonate solution, dried (MgSO4) and concentrated under reduced pressure, The residue was purified by silica gel column chromatography using EtOAc:Hexanes 1:20 to give the desired sulfone (1132l).

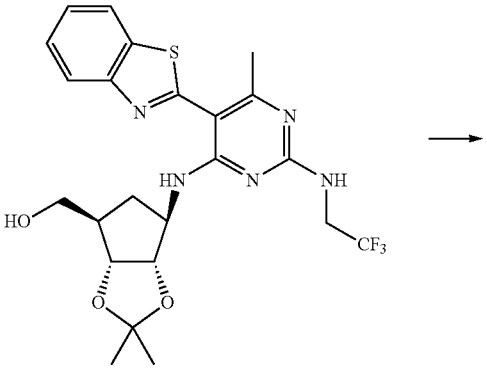
Triethylamine (0.022 ml) was added to a mixture of the iodide (1132l; 0.034 g), (2-tributylstannylbenzothiazole (0.037 g), copper(I) iodide (0.003 g) and $PdCl_2(PPh_3)_2$ (0.006 g) in dioxane (2 ml) and the reaction mixture was heated to 100 C, under an atmosphere of nitrogen for 1 h. After cooling, additional portions of the stannane, copper iodide, palladium catalyst and triethylamine were added and the mixture heated for a further 1 h. after cooling, the reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with water, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:10) to give the benzthiazole (1132m; 0.012 g) as a white solid.

Cyclopropylmethylamine (0.050 ml) was added to a solution of the sulfone (1132m; 0.012 g) and the mixture was heated to 110 C (oil bath temp.) for a period of 4 h., under an atmosphere of nitrogen. The volatiles were removed under reduced pressure to provide the desired amine (1132n) used without purification in the next step.

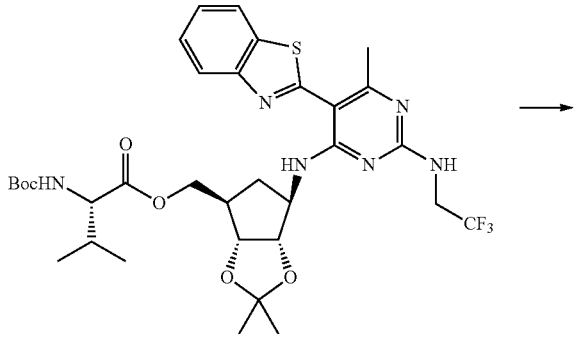
To all the material (1132n) from the previous step was added THF (1 ml), MeOH (1 ml) and 6N aq. HCl (0.5 ml). The resulting mixture was allowed to stand at room temperature for 2 h. The volatiles were removed under reduced pressure and the solid was washed with ether to provide the triol (1132, HCl salt; 0.0047 g) as a white solid.

Example 1133

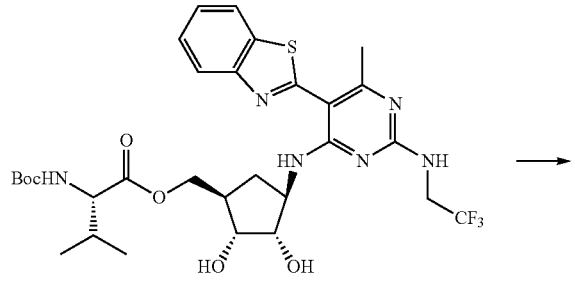
Procedure Z18



1015a



1133a



1133b

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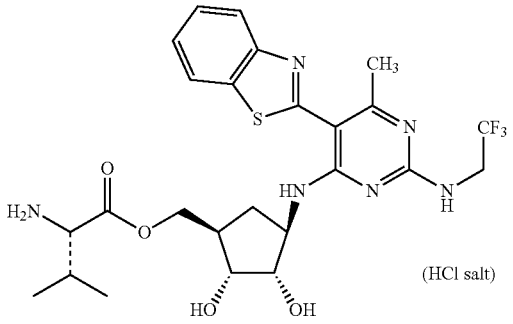


1133

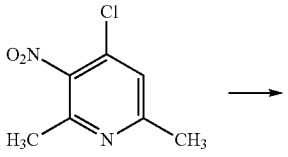
Triethylamine (0.082 ml) was added to a stirred mixture of the primary alcohol (1015a; 0.08 g), Boc-L-Val-OH (0.0423 g) and BOP reagent (0.086 g) in dichloromethane (3 ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. the organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and the volatiles were removed under reduced pressure. the residue was purified by silica gel column chromatography to give the desired ester (1133a; 0.046 g) as a white solid.

4M HCl in dioxane (5 ml) was added dropwise to a stirred solution of the dimethylketal (1133a; 0.040 g) in methanol (3 ml) and water (5 ml) while cooled in an ice bath. The resulting mixture was stirred for 2.5 h and solid sodium bicarbonate was added. aqueous work-up and silica gel column chromatography gave the desired diol (1133b; 0.0361 g) as a white solid.

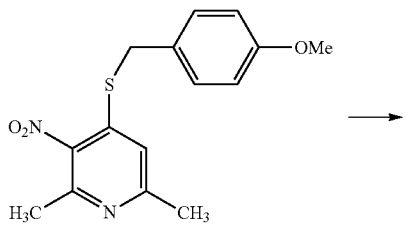
To the protected aminoacid ester (1133b; 0.035 g) in a mixture of methanol (3 ml) and water (5 ml) was added 4M HCl in dioxane (5 ml) while cooled in an ice bath. The resulting mixture was allowed to warm to room temperature overnight. The volatiles were removed under a stream of nitrogen to give the desired HCl salt (1133; 0.0286 g) as white solid.

Example 1134

Procedure Z19



1134a



1134b

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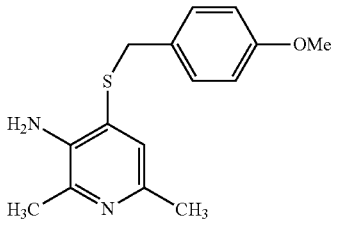
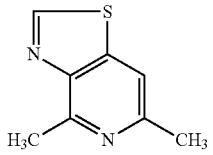
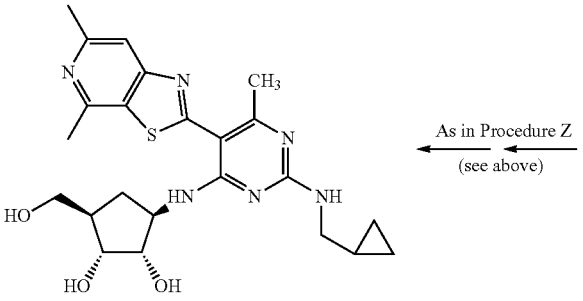


1134c



1134d



1134 (HCl salt)

Sodium hydride (0.223 g of a 60% dispersion in mineral oil) was added to a mixture of the chloride (as prepared according to J. Med. Chem. 1998, vol 41(22), pp. 4408-4420; 1134a; 0.691 g) and 4-methoxybenzylthiol (0.860 g) in anhydrous THF (10 ml) and the resulting mixture was stirred at room temperature for a period of 1 h. Saturated aq. sodium bicarbonate was added and the organics were extracted into methylene chloride (×3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the desired sulfide (1134b; 1.019 g) as a pale-yellow solid.

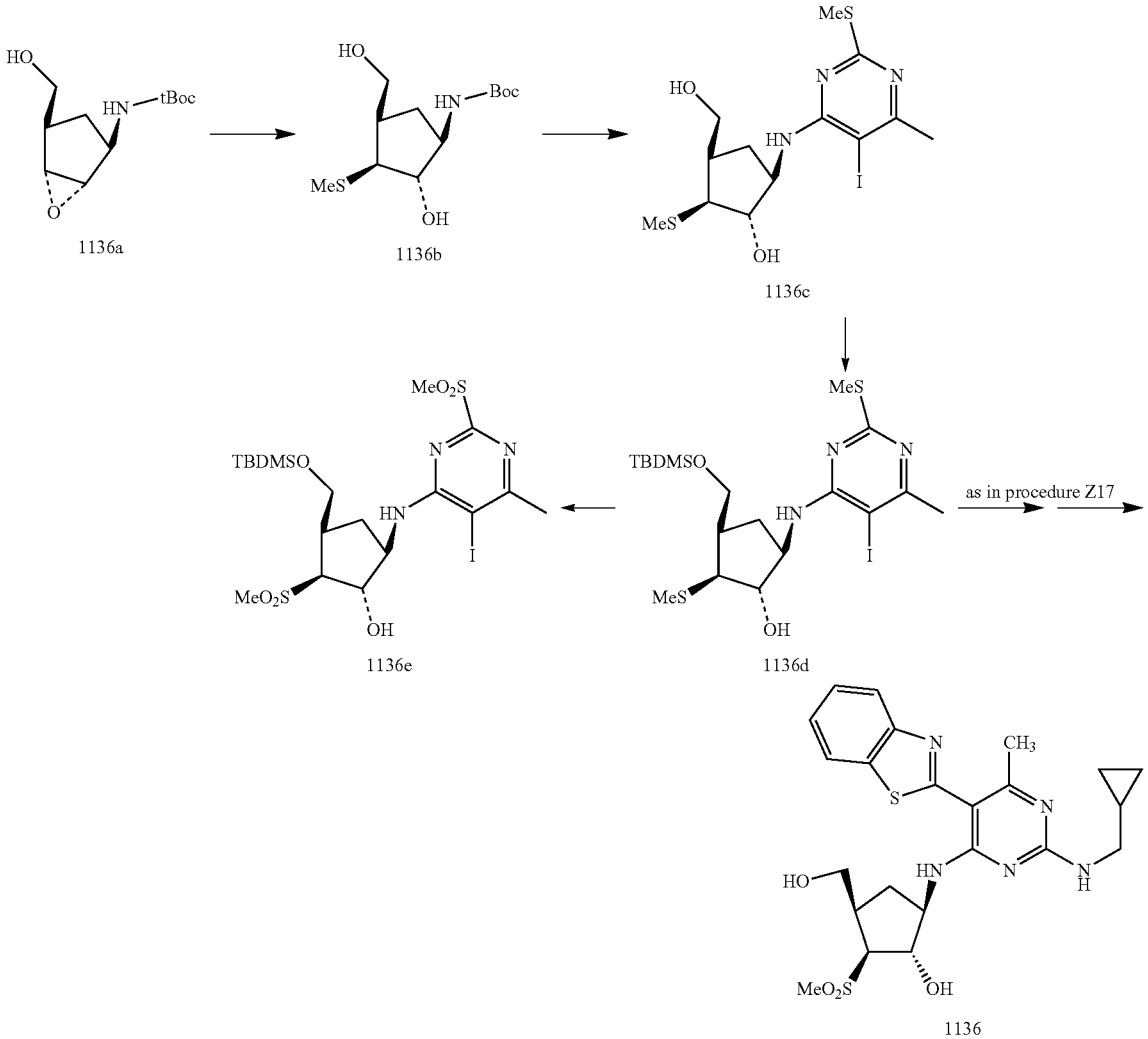
To the nitro compound (1134b, 1.06 g) was added ethanol (10 ml) and 10% Pd—C (0.50 g) was added and the resulting suspension was stirred under an atmosphere of hydrogen (balloon) at room temperature overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The filtrate was concentrated under reduced pressure to provide the desired amine (1134c) used in the next step without purification.

Formic acid (10 ml) was added to the amine (1134c) and the resulting mixture was heated (150 C; oil bath temp.) for a period of 3 h. After cooling, TFA (30 ml) was added and the mixture heated (150; oil bath temperature) overnight. After cooling, the volatiles were removed under reduced pressure and the residue was partitioned between methylene chloride and sat. aq. sodium bicarbonate. The organic phase was separated, dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography to give the pyridylthiazole (1134d; 0.201 g).

Using the procedures set forth in procedure Z above 1134d was transformed into 1134.

Example 1136

Procedure Z20



To the epoxide (prepared according to J.A.C.S. 2005, 127(51), pp. 18143-18149; 1136a; 1.00 g) in ethanol was added NaSMe (0.379 g) and the resulting mixture was stirred at room temperature overnight, under an atmosphere of nitrogen. The volatiles were removed under reduced pressure and the residue partitioned between EtOAc and water. the organic phase was separated, dried (MgSO4) and concentrated. The residue was purified by silica gel column chromatography to give the diol (1136b; 0.421 g) as a white solid.

4M HCl in dioxane (5 ml) was added to the carbamate (1136b; 0.400 g) and the mixture was allowed to stand at room temperature for 2 h. the volatiles were removed under reduced pressure and ethanol (7 ml), the pyrimidine (324d; 0.535 g) and triethylamine (1.04 ml) were added and the resulting mixture was heated to reflux overnight. After cooling, the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography to give the desired adduct (1136c; 0.409 g)

DMAP (0.011 g) was added to a mixture of the diol (1136c; 0.400 g), TBDMSCl (0.150 g), and triethylamine (0.151 ml) in dichloromethane (10 ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the silyl ether (1136d; 0.362 g).

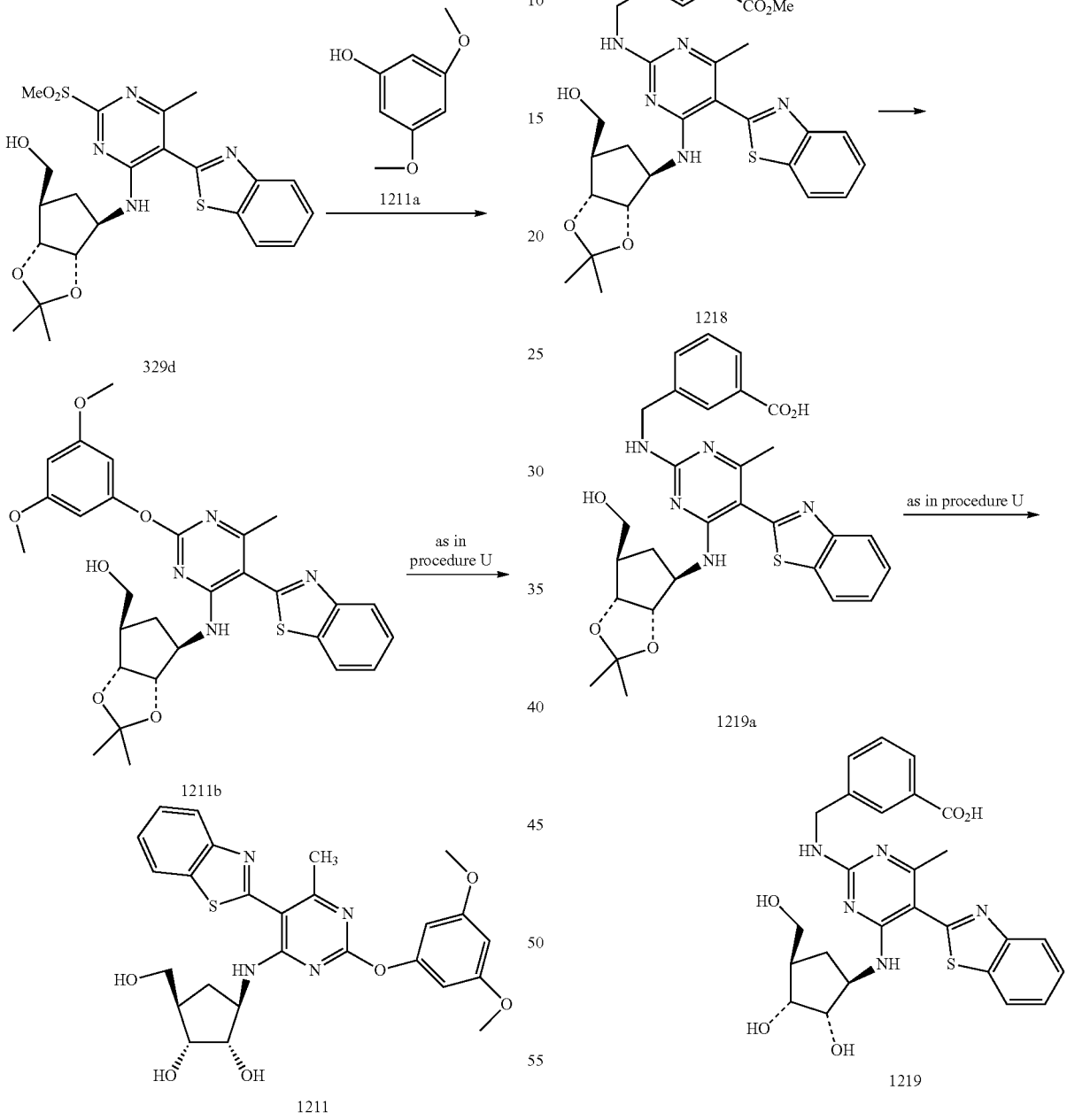
To the di-methylsulfide (1136d; 0.195 g) and sodium bicarbonate (0.295 g) in dichloromethane was added MCPBA (0.394 g of 77% pure material) and the resulting suspension was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% sodium thiosulfate. The organic phase was separated, dried (MgSO4) and concentrated under reduced pressure to give the di-sulfone (1136e; 0.184 g).

$PdCl_2(PPh_3)_2$ (0.0403 g) followed by CuI (0.020 g) were added to mixture of the iodide (1136e; 0.184 g), 2-tributylstannylbenzothiazole (0.252 g) and triethylamine (0.156 ml) in dioxane (3 ml). The resulting mixture was heated to 100 C for 2 h. After cooling, aqueous work-up and silica gel column chromatography gave the desired adduct (1136f; 0.096 g).

Using the benzthiazole (1136f) and the procedures set forth in general procedure Z17, 1136 was obtained.

Example 1211

Procedure Z21



A mixture of sulfone (329d; 0.100 g) and the phenol (1211a; 0.157) in acetonitrile (5 ml) was heated to 100 C (oil bath temperature) under an atmosphere of nitrogen, overnight. After cooling, the volatiles were removed under reduced pressure. The residue was purified by silica gel plate chromatography to give the desired ether (1211b; 0.045 g).

1211b was transformed into 1211 as carried out for the conversion of 328 to 329 in procedure U.

Example 1219

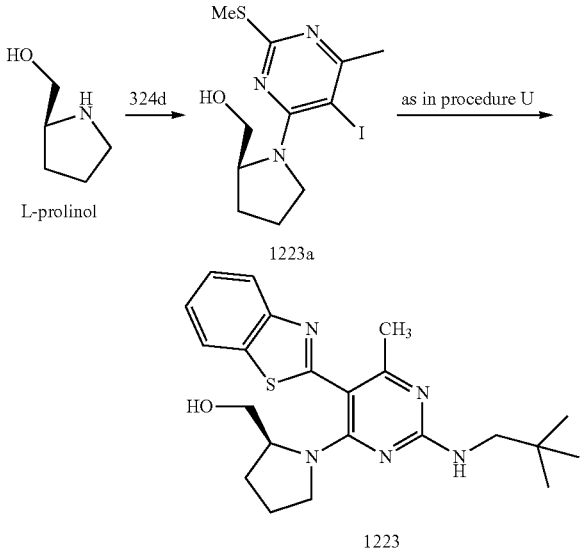
Procedure Z21

To the methyl ester (1218) was added LiOH:H_2O (2 eq.) in dioxane and water (1:1) and the resulting mixture was stirred overnight at room temperature. The reaction was acidified with acetic acid and the organics extracted into EtOAc. The organic phase was separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure to provide the acid (1219a).

1219a was transformed into 1219 as carried our for the conversion of 328 to 329 in procedure U.

Example 1223

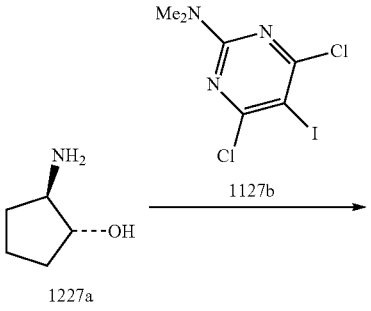
Procedure Z22



Using L-prolinol rather than the carbasugar, 1223 was produced via procedure U.

Example 1227

Procedure Z23



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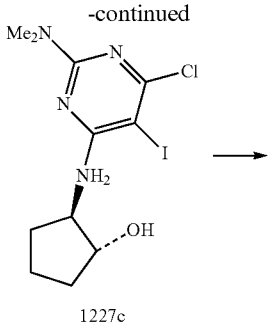
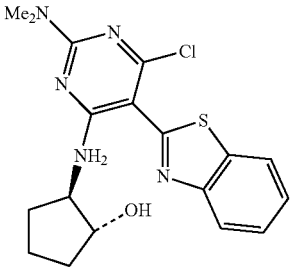


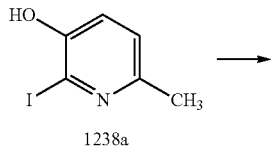


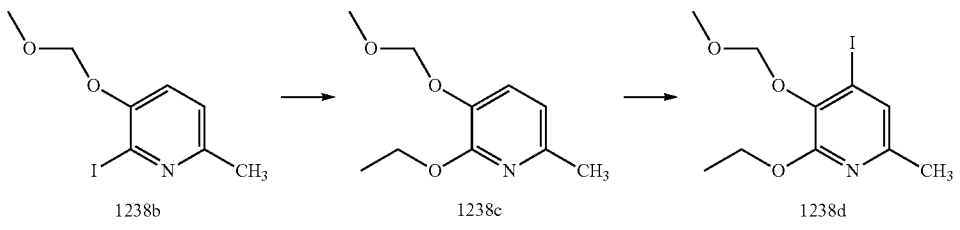
A mixture of the amino alcohol (rac-1227a; 0.477 g), pyrimidine (1227b; 1.00 g) and triethylamine (1.54 ml) in ethanol (20 ml) was refluxed under an atmosphere of nitrogen, overnight. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography to give the adduct (1227c).

Triethylamine (0.292 ml) was added to a mixture of the iodide (1227c; 0.200 g), 2-tributylstannylbenzothiazole (0.444 g), copper iodide (0.040 g) and $PdCl_2(PPh_3)_2$ in dioxane (20 ml) and the mixture was heated to 110 C under an atmosphere of nitrogen for 2 h. After cooling, the mixture was filtered through a pad of celite and the solid was washed thoroughly with EtOAc. The filtrate was concentrated and the residue was purified by silica gel column chromatography to give the benzthiazole (1227; 0.090 g).

Example 1238

Procedure Z24





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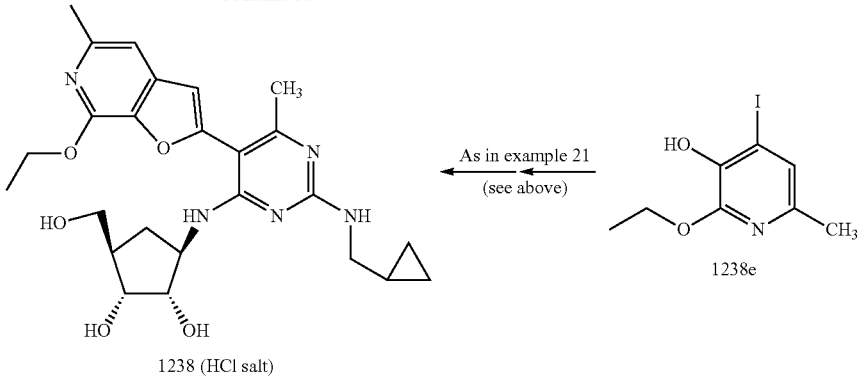


To a mixture of the phenol (1238a; 2.00 g) and Hunigs base (2.2 ml) in dichloromethane (20 ml) was added chloromethylmethyl ether (1.29 ml) while cooled in an ice bath, under an atmosphere of nitrogen. The reaction mixture was allowed to reach room temperature, overnight. Solid sodium bicarbonate is added and the suspension is partitioned between methylene chloride and water. the organic phase was separated, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the desired ether (1238b; 7.30 g)

Sodium ethoxide (1.48 g) was added to anhydrous ethanol (30 ml) and stirred for 10 min. at room temperature before the addition of the iodide (1238b; 1.22 g) and copper(I) bromide (0.125 g). The resulting mixture was heated to 90 C for 2.5 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography to provide the desired adduct (1238c; 0.69 g).

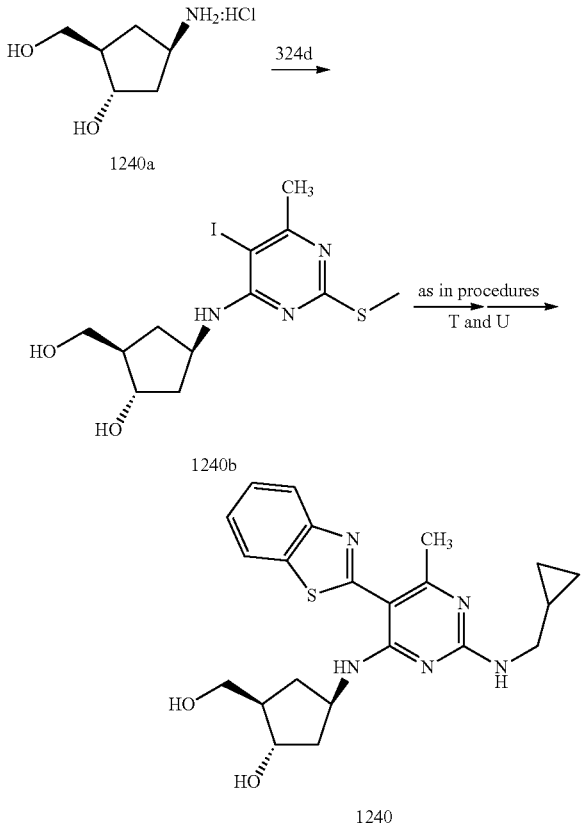
n-BuLi (2.9 ml of a 2.5M solution in hexanes) was added dropwise to a stirred solution (THF; 20 ml) of the MOM ether (1238c; 1.20 g) at −78 C, under an atmosphere of nitrogen. The resulting mixture was stirred at this temperature for a period of 1 h., before the addition of iodine (1.70 g) in THF (10 ml). After stirring for a further 1 h., 1M aq. ammonium chloride and the mixture was allowed to warm to room temperature then partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried (MgSO4) and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired iodide (1238d; 1.763 g).

TFA (4 ml) was added to a dichloromethane (16 ml) solution of the acetal (1238d; 1.60 g) while cooled in an ice bath, under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature overnight and the volatiles were removed under reduced pressure and the residue partitioned between dichloromethane and sat. aq. sodium bicarbonate. The organic phase was separated, dried (MgSO4) and concentrated under reduced pressure to give the desired pyridol (1238e; 1.292 g)

The iodopyridol (1238e) was transformed into 1238 using the chemistry set forth in example 21, above.

Example 1240

Procedure Z25

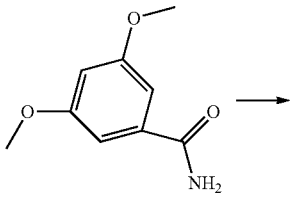


A mixture of the hydrochloride salt (1240a; 2.6 mmol; prepared as in J.A.C.S., 2005, 127(51), p 18143), pyrimidine (324d; 0.937 g) and triethylamine (1.81 ml) in ethanol (10 ml) was refluxed under an atmosphere of nitrogen for a period of 12 h. After cooling, the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography to give the desired adduct (1240b; 0.844 g).

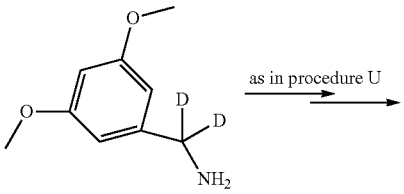
Using the chemistries outlined in procedures T and U above the diol (1240) was transformed into 1240.

Example 1244

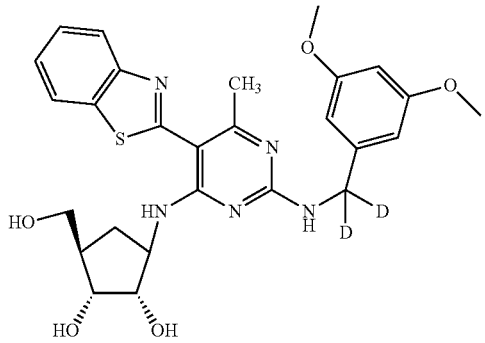
Procedure Z26



1244a



1244b



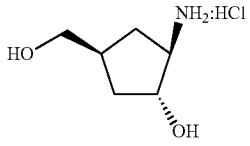
1244

Lithium aluminium deuteride (0.42 g) was added in portions to a THF (20 ml) solution of the carboxamide (1244a; 1.63 g) at room temperature, under an atmosphere of nitrogen. 10% aq. NaOH followed by water and dichloromethane were added and the mixture was filtered through a pad of celite. The solid was washed thoroughly with THF and methanol. The filtrate was concentrated. Toluene was added (×3) and concentrated to give the amine (1244b)

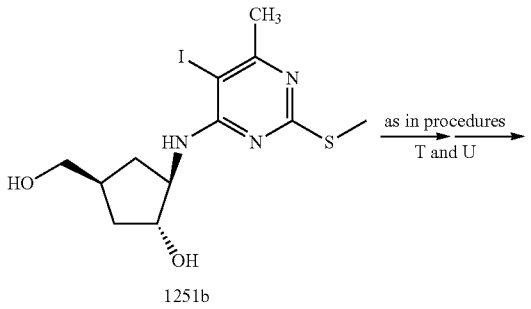
The amine (1244b) was converted into 1244 using the chemistry described in procedure U.

Example 1251

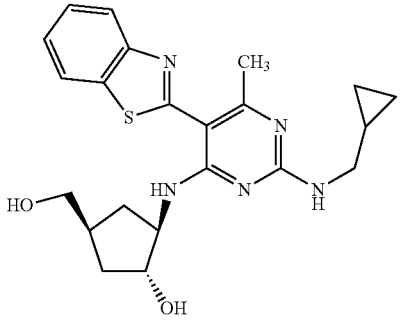
Procedure Z27



1251a



1251b



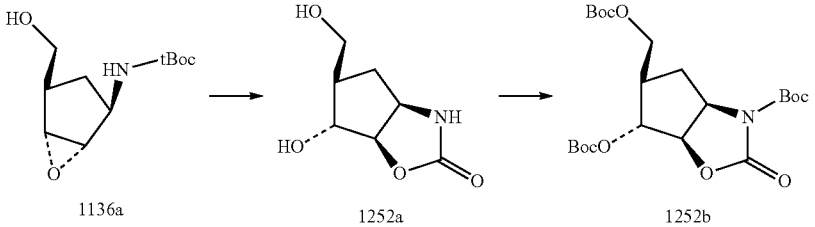
1251

A mixture of the hydrochloride salt (1251a; 1 equivalent with respect to 324d; prepared as in J.A.C.S., 2005, 127(24), p 8846), pyrimidine (324d; 0.288 g) and triethylamine (0.61 ml) in ethanol (8 ml) was refluxed under an atmosphere of nitrogen for a period of 12 h. After cooling, the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography to give the desired adduct (1251b; 0.200 g).

Using the chemistries outlined in procedures T and U above the diol (1251b) was transformed into 1251.

Example 1252

Procedure Z28



1136a

1252a

1252b

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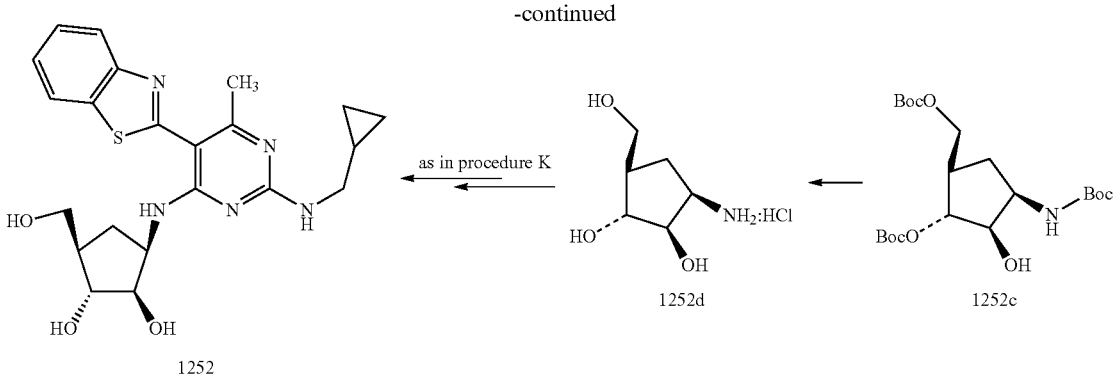


To the epoxide (1136a; 1.00 g) in methylene chloride (15 ml) was added (1S)-(+)-10-camphorsulfonic acid (0.101 g; 0.1 eq.) and the resulting mixture was stirred at room temperature for 12 h. Sat. aq. sodium bicarbonate was added and the organics were extracted into methylene chloride (×3). The combine organic phases were dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to provide the diol (1252a; 0.494 g).

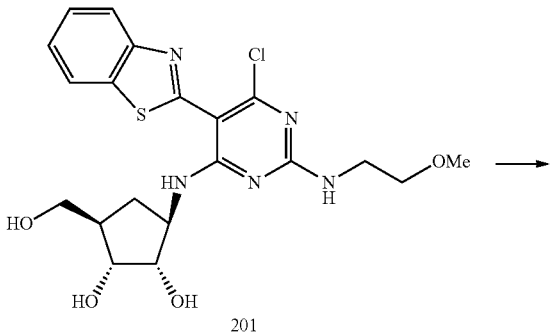
Triethylamine (1.2 ml) followed by DMAP (0.068 g) were added to the diol (0.494 g) in THF (40 ml) and the resulting mixture was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography to give the desired adduct (1252b; 1.08 g).

Caesium carbonate (0.17 g) was added to the oxazolidinone (1252b; 1.08 g) in methanol (25 ml) and the resulting mixture was stirred at room temperature overnight. Sat. aq. ammonium chloride was added and the organics were extracted into methylene chloride. The organic phase was dried (MgSO4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the alcohol (1252c; 0.67 g)

The alcohol (1252c) was converted to the triol (1252d) with 4M HCl in dioxane and further converted into 1252 using the appropriate steps outlined in general procedure K.

Example 1301

Procedure Z29



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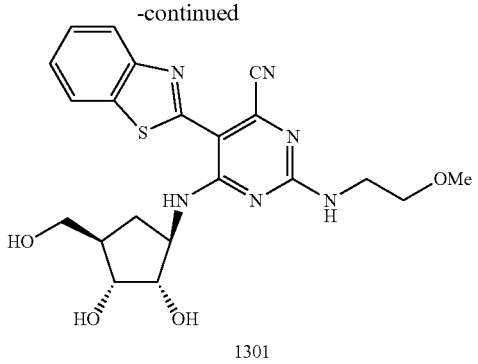
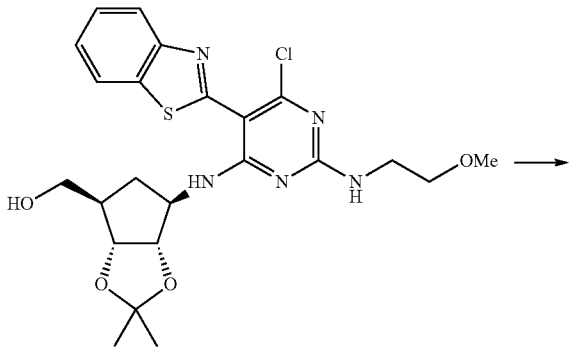


Compound 201 (100 mg, 0.21 mmol) was combined with $Zn(CN)_2$ (300 mg), Pd(PPh3)4 (50 mg), and NMP (2 mL). The reaction was stirred at 100 C overnight. The reaction was poured into water and filtered. The solids were washed with water and methylene chloride. After drying the solids were stirred in MeOH (2 mL) and then filtered. The methanol was concentrated to provide the product, 1301 (100 mg). [M+H]=457.3.

Example 1302

Procedure Z30



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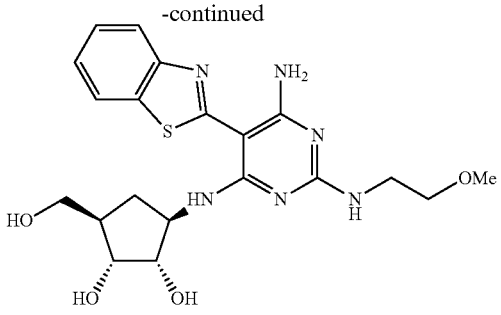
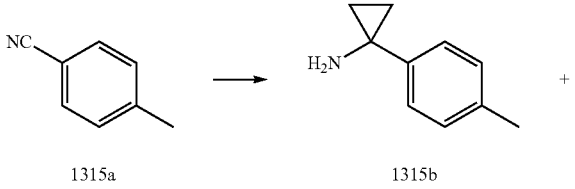


1302

Compound 1302a (100 mg, 0.197 mmol) was dissolved in ammonium hydroxide (3 mL) and dioxane (3 mL) and refluxed for 48 hrs. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide 40 mg of the acetonide protected material [M+H] =487.4. This material was dissolved in MeOH (3 mL), 4M HCl dioxane (1 mL) and water (0.1 mL) and stirred for 3 hours at room temperature. The reaction was concentrated to provide the desired product 1302 (40 mg). [M+H]=447.2

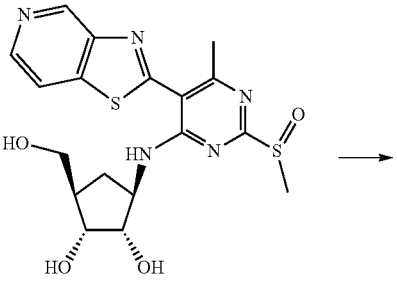
Example 1315

Procedure Z31

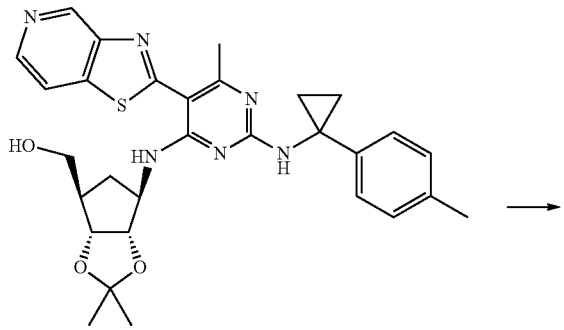


1315a

1315b



523f



1315c

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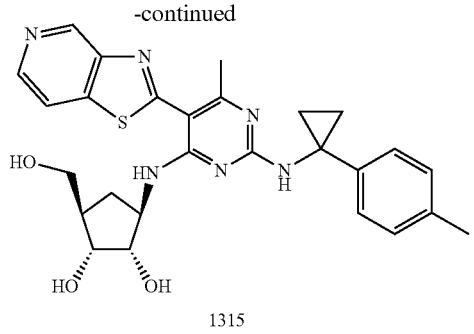


1315

Step 1:

See *Journal of Organic Chemistry,* 2003, 68, 7133 for the synthesis of similar derivatives from corresponding benzonitriles. [M+H]=148.2

Step 2:

See Procedure Z for similar experimental.

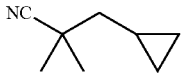
Step 3:

See Procedure Z for similar experimental.

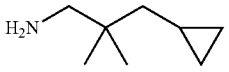
Example 1318

Procedure Z32

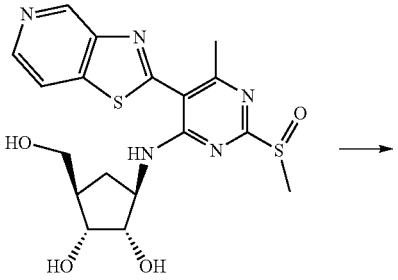
1318a



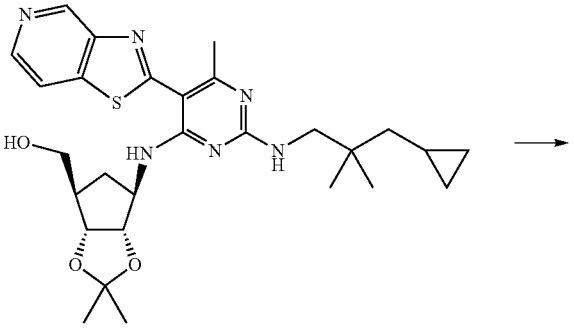
1318b



1318c



523f



1318d

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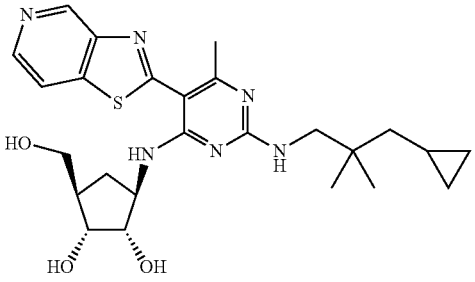


1318

Step 1:

A solution of 2M LDA (17 mL, 35 mmol) was cooled to −78 C and isobutyronitrile (1318a, 2.0 g, 30 mmol) was added dropwise in THF (20 mL). After the reaction was stirred for 1 hr at −78 C and 1 hr at 0 C, a solution of cyclopropylmethyl bromide (4.69 g, 35 mmol) was added dropwise in THF (15 mL). The resulting solution was stirred overnight at room temperature and then quenched with saturated ammonium chloride and extracted with diethyl ether. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (hexanes→20% Et2O/hexanes) to provide 2.1 g of the product 1318b.

Step 2:

Compound 1318b (900 mg, 7.31 mmol) was dissolved in diethyl ether (10 mL) and treated with lithium aluminum hydride (300 mg). The mixture was refluxed overnight and then slowly quenched with 1N NaOH. The solids were filtered and washed with ether. The combined ether layers were dried over sodium sulfate and concentrated to provide the desired product 1318c (700 mg).

Step 3:

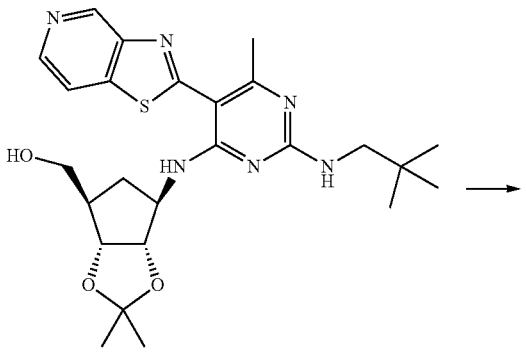
See Procedure Z for similar experimental.

Step 4:

See Procedure Z for similar experimental.

Example 1321

Procedure Z33



536

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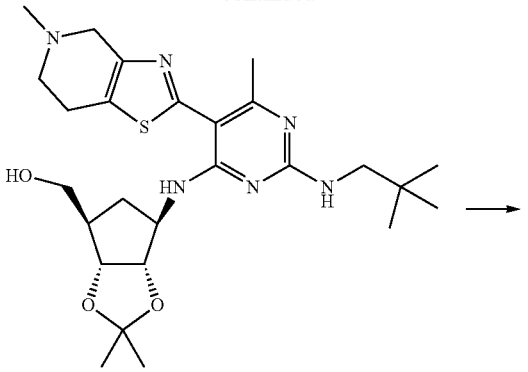
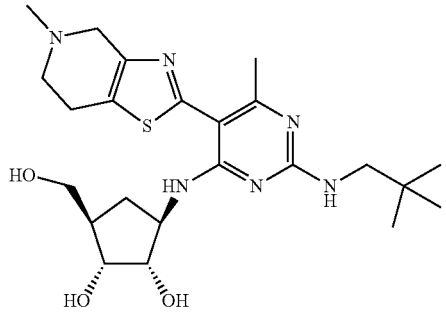


1321a



1321

Step 1:

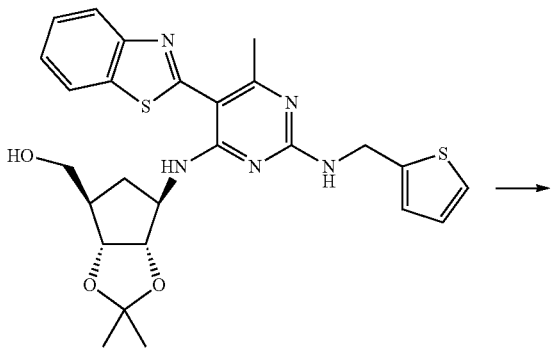
Compound 536 (60 mg, 0.120 mmol) was dissolved in acetone (3 mL) and iodomethane (0.3 mL). The solution was stirred at 80 C for 2 hours. The solvent was evaporated and the product was used without purification (~65 mg). [M+H] =513.5. The residue was dissolved in THF (5 mL) and water (5 mL) and treated with sodium borohydride (0.2 g). The reaction was stirred overnight and then quenched with saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide 1321a (60 mg). [M+H]=517.6

Step 2:

See Procedure Z for similar experimental.

Example 1327

Procedure Z34



328

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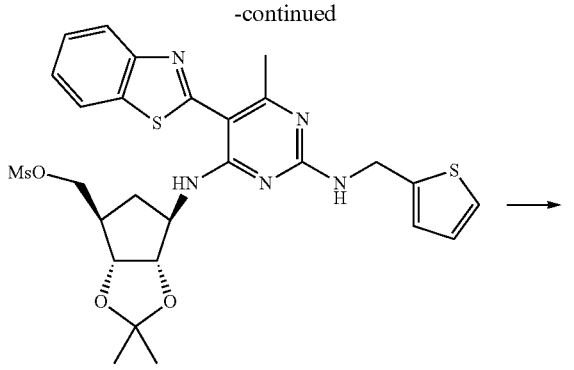
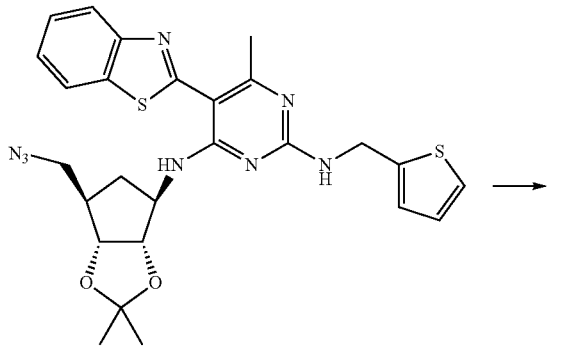
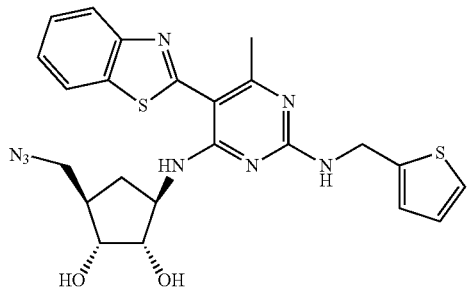


1327a



1327b



1327

Compound 328 was synthesized using procedure U.

Step 1:

Compound 328 (370 mg, 0.707 mmol) was dissolved in methylene chloride (10 mL) and triethylamine (0.1 mL) and cooled to 0 C. Methanesulfonyl chloride (89 mg, 0.78 mmol) was added dropwise in methylene chloride (1 mL) and the reaction was stirred for 1 hour at room temperature. The reaction was treated with water and the organic layer was dried over sodium sulfate and concentrated to provide the desired product 1327a (380 mg). [M+H]=602.5

Step 2:

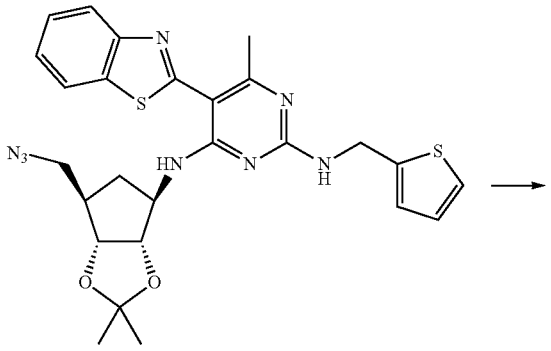
Compound 1327a (380 mg, 0.62 mmol) was dissolved in DMF (5 mL) and treated with sodium azide (500 mg). The reaction was stirred at 90 C for 3 hours and then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated to provide compound 1327b (350 mg). [M+H]=549.48

Step 3:

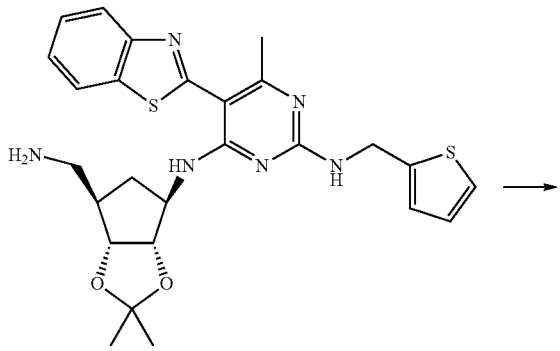
See Procedure Z for similar experimental.

Example 1328

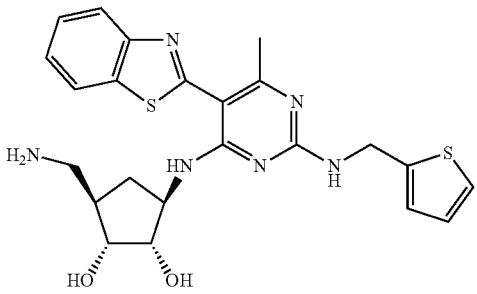
Procedure Z35



1327b



1328a



1328

Step 1:

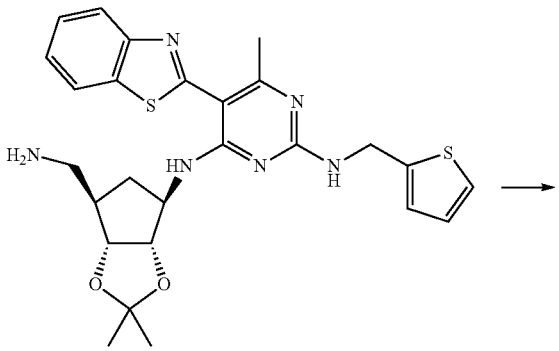
Compound 1327b (100 mg, 0.182 mmol) was dissolved in THF (3 mL) and treated with triphenylphosphine (95 mg, 0.36 mmol). The reaction was stirred for 15 minutes and then treated with ammonium hydroxide (0.5 mL) and refluxed for 2 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was treated with 4M HCl dioxane (0.5 mL). The solids were filtered to provide the desired product 1328a (75 mg). [M+H]=523.5

Step 2:

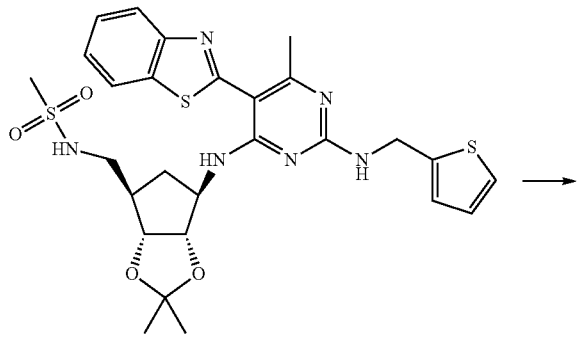
See Procedure Z for similar experimental.

Example 1330

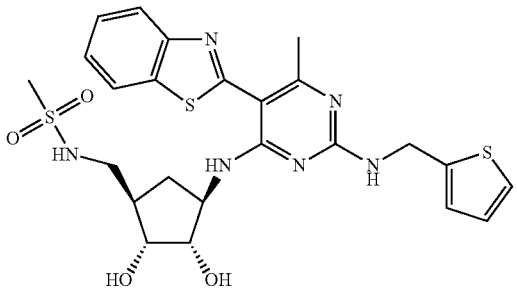
Procedure Z36



1328a



1330a



1330

Step 1:

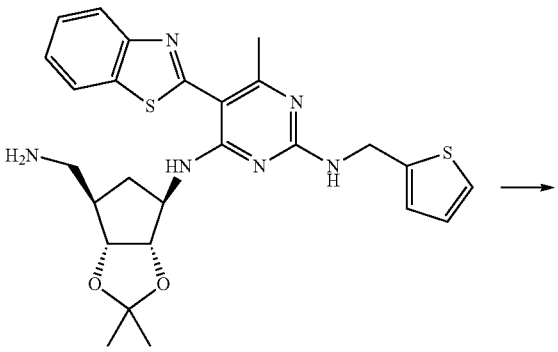
Compound 1328a (65 mg, 0.124 mmol) was dissolved in methylene chloride (5 mL) and treated with triethylamine (13 mg, 0.124 mmol) and methanesulfonyl chloride (15 mg, 0.124 mmol). The reaction was stirred for 2 hours at room temperature and then quenched with water. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexane/ethyl acetate→ethyl acetate). Isolated 45 mg of product, 1330a. [M+H]=601.5

Step 2:

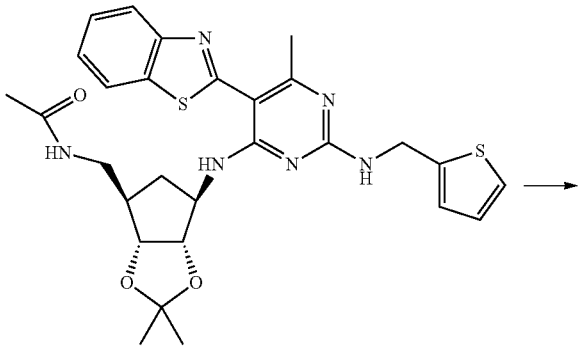
See Procedure Z for similar experimental.

Example 1331

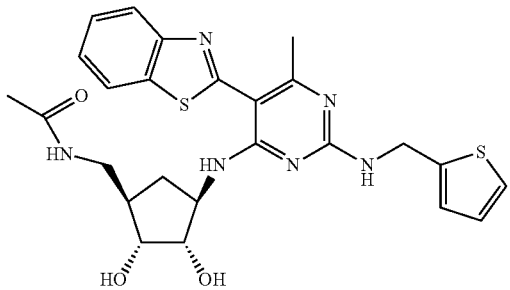
Procedure Z37



1328a



1331a



1331

Step 1:

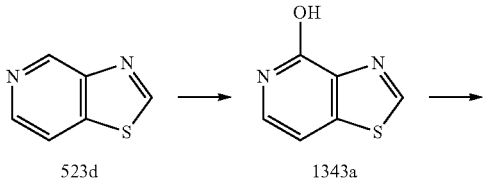
Compound 1328a (65 mg, 0.124 mmol) was dissolved in THF (5 mL) and 1M NaOH (3 mL) and treated with acetic anhydride (0.1 mL). After 2 hours the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate) to provide 45 mg of compound 1331a. [M+H]=565.5

Step 2:

See Procedure Z for similar experimental.

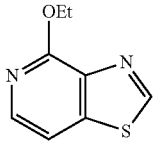
Example 1343

Procedure Z38

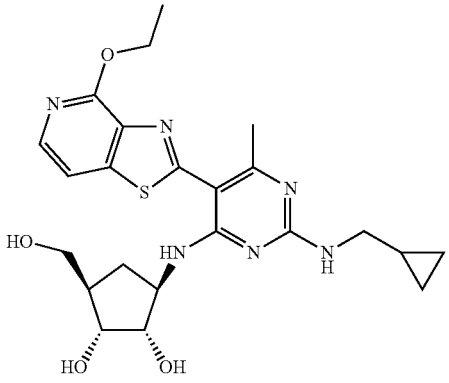


523d

1343a



1343b



1343

Step 1:

Compound 523d (1.5 g, 10.94 mmol) was suspended in methylene chloride (50 mL) and 77% mCPBA (3.77 g, 16.4 mmol) was added. The reaction was stirred for 2 hours and then the solvent was removed. The solids were washed with methylene chloride (2×). The solids were triturated with ethyl acetate to provide 700 mg of clean product 1343a and 700 mg with slight mCPBA impurities. [M+H]=153.16

Step 2:

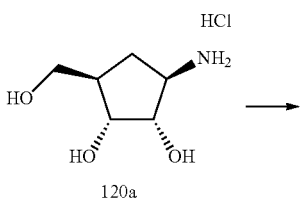
Compound 1343a (400 mg, 2.61 mmol) was dissolved in chloroform (15 mL) and treated with Etl (2 mL) and silver carbonate (1.0 g, 3.63 mmol) at reflux. After 3 hours the reaction was filtered and concentrated. The residue was purified by column chromatography (30% ethyl acetate/hexanes) to provide 140 mg of compound 1343b.

Step 3:

The product 1343 was synthesized from 1343b using chemistry similar to that found in procedure Z.

Example 1350

Procedure Z39



120a

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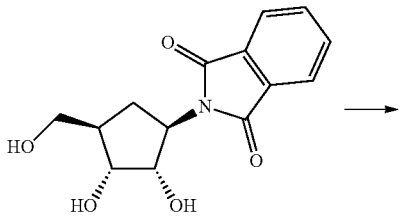
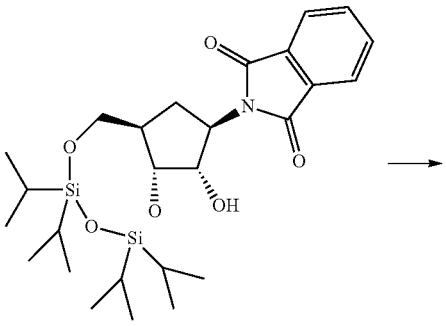
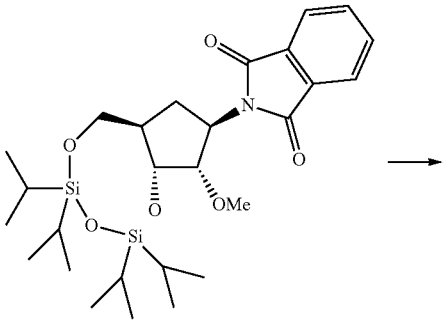


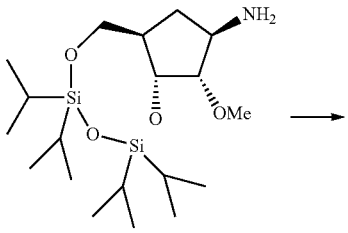
1350a



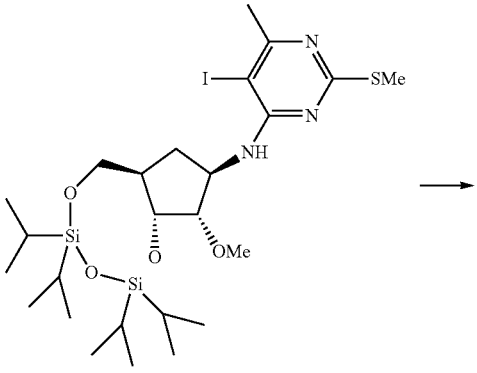
1350b



1350c



1350d



1350e

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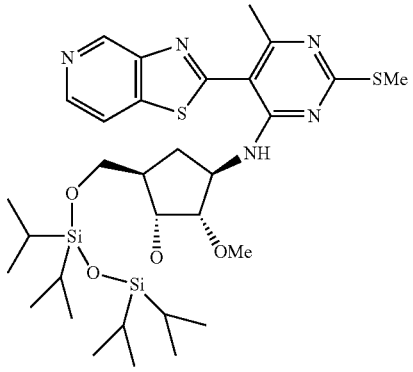
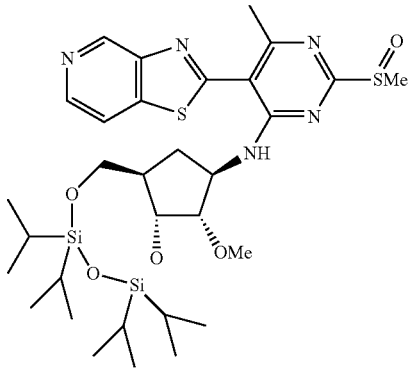
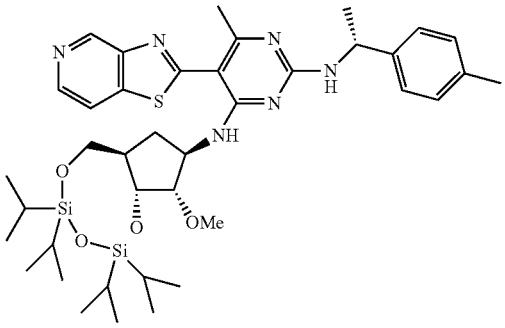


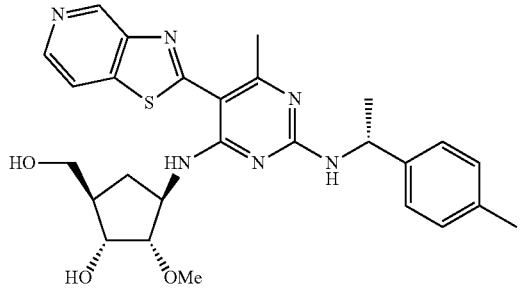
1350f



1350g



1350h



1350

Step 1:

Compound 120a (3.0 g, 16.39 mmol) was combined with phthalic anhydride (2.41 g, 16.39 mmol) and DIEA (3.81 mL, 21.3 mmol) and stirred at 140 C for 5 hours. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and 1N HCl. The aqueous layer was saturated with brine and extracted with ethyl acetate several times. The combined organic layers were dried over sodium sulfate and concentrated to provide 2.5 g of compound 1350a. [M+Na]=300.3

Step 2:

Compound 1350a (2.0 g, 7.2 mmol) was combined with imidazole (1.53 g, 21.6 mmol) and dissolved in DMF (15 mL). A solution of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.27 g, 7.2 mmol) in DMF (5 mL) was added dropwise and the reaction was stirred for 12 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (4:1 hexanes/ethyl acetate) to provide 3.0 g of the product 1350b. [M+H]=520.4

Step 3:

Compound 1350b (2.2 g, 4.2 mmol) was dissolved in DMF (15 mL) and cooled to 0 C. 60% NaH (169 mg, 4.2 mmol) was added and the reaction was stirred for 20 minutes at room temperature. At this point iodomethane (1 mL) was added and the reaction was stirred for 3 hours and then quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (5:1 hexanes/ethyl acetate) to provide 1.5 g of product 1350c.

Step 4:

Compound 1350c (1.5 g, 2.8 mmol) was dissolved in ethanol (10 mL) and diethyl ether (10 mL) and treated with hydrazine (0.5 mL). The reaction was stirred overnight at rt and then filtered. The filtrate was concentrated and triturated with 1:1 ether/ethanol to provide 1350d (1.1 g). [M+H]=404.4

Step 5:

Reaction was performed in a similar manner to Procedure U, Step 1.

[M+H]=668.32

Step 6:

Reaction was performed in a similar manner to Procedure Z, Step 4.

[M+H]=676.47

Step 7:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=692.4

Step 8:

Reaction was performed in a similar manner to Procedure Z, Step 6.

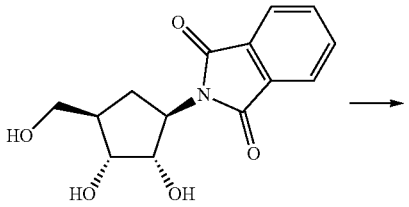
[M+H]=763.62

Step 9:

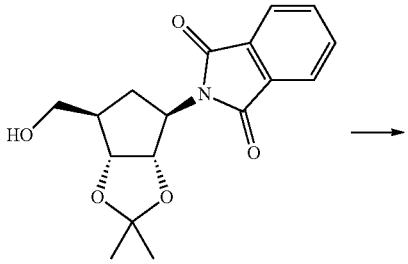
Compound 1350h (75 mg, 0.098 mmol) was dissolved in THF (5 mL) and treated with TBAF (26 mg, 0.098 mmol). After 2 hours the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (10:1 ethyl acetate/methanol) to provide the desired product 1350 (28 mg). [M+H]=521.37

Example 1367

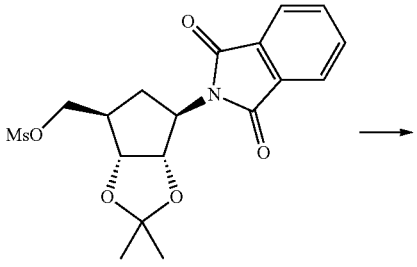
Procedure Z40



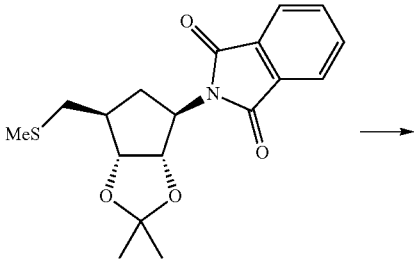
1350a



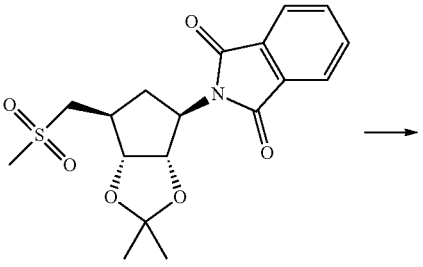
1367a



1367b



1367c



1367d

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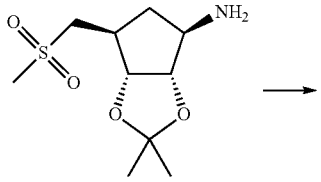
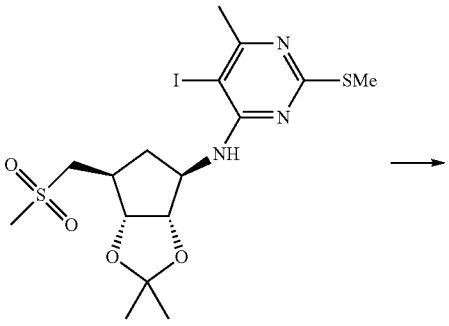
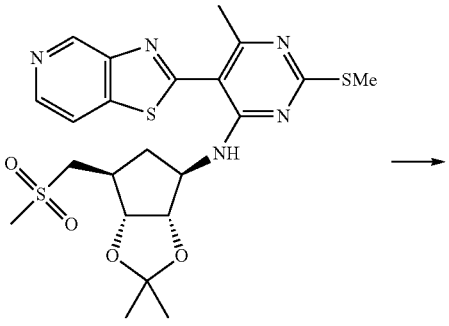


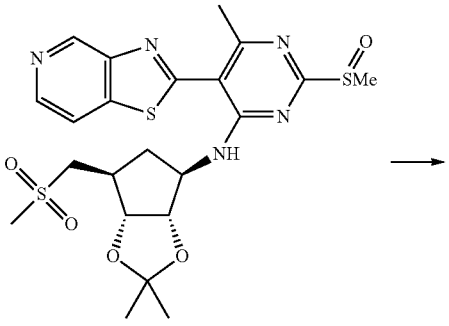
1367e



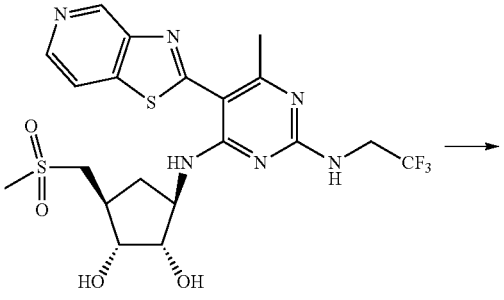
1367f



1367g



1367h



1367i

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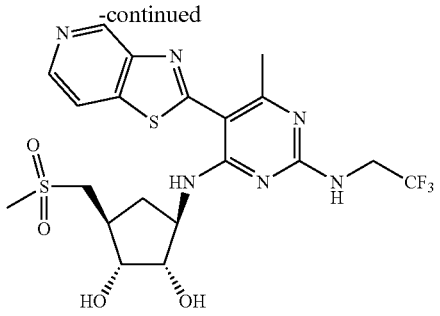


1367

Step 1:

Compound 1350a (1.3 g, 4.6 mmol) was dissolved in acetone (30 mL) and treated with 2,2-dimethoxypropane (2 mL) and methanesulfonic acid (1 mL). After 5 hours the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide 1.2 g of compound 1367a. [M+Na]=340.2

Step 3:

Compound 1367a (1.2 g, 3.77 mmol) was dissolved in methylene chloride (40 mL) and triethylamine (0.7 mL, 5 mmol). The reaction was cooled to 0 C and then methanesulfonyl chloride (517 mg, 4.5 mmol) was added dropwise in methylene chloride (5 mL). After stirring overnight the reaction was quenched with water. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide 1.25 g of compound 1367b. [M+Na] =418.21

Step 4:

Compound 1367b (1.1 g, 2.7 mmol) was dissolved in DMA (10 mL) and was treated with sodium thiomethoxide (290 mg, 4.15 mmol). The reaction was stirred for 5 hours and then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated to provide 1.0 g of compound 1367c that was used without purification.

Step 5:

Compound 1367c (1.0 g, 2.8 mmol) was dissolved in methylene chloride (20 mL) and treated with 77% mCPBA (3.2 g, 14.4 mmol). After stirring overnight the reaction was quenched with 1M potassium carbonate and extracted with methylene chloride. The organic layers were dried over sodium sulfate and concentrated to provide compound 1367d that was used without purification (550 mg).

Step 6:

Compound 1367d (550 mg, 1.45 mmol) was suspended in ethanol (10 mL) and treated with hydrazine monohydrate (0.5 mL). After stirring at 70 C for 30 minutes (to solubilize the reaction), the temperature was reduced to rt and the reaction was stirred overnight. The reaction was filtered and the filtrate was concentrated to provide compound 1367e (330 mg). [M+H]=250.18

Step 7:

Reaction was performed in a similar manner to Procedure U, Step 1.

[M+H]=514.14

Step 8:

Reaction was performed in a similar manner to Procedure F, Step 2.

[M+H]=522.20

Step 9:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=538.23

Step 10:

Reaction was performed in a similar manner to Procedure Z, Step 6.

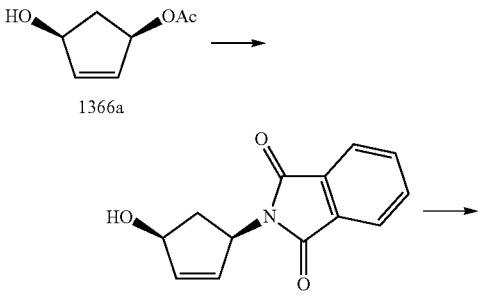
[M+H]=573

Step 11:

The product 1367 was synthesized from 1367i using chemistry similar to that found in procedure Z.

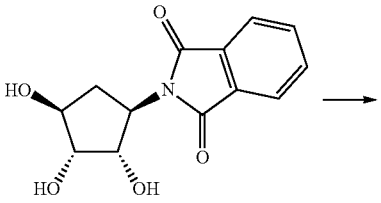
Example 1366

Procedure Z41

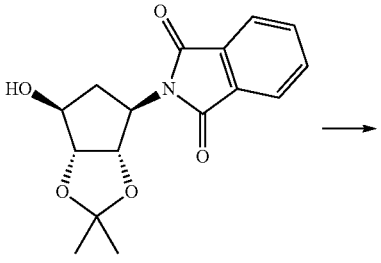


1366a

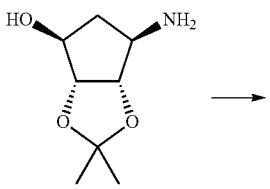
1366b



1366c



1366d



1366e

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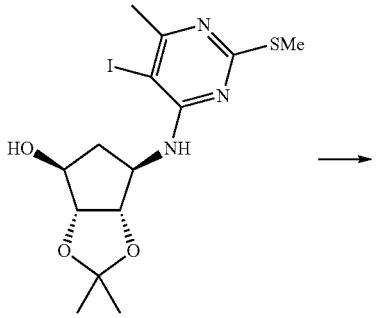
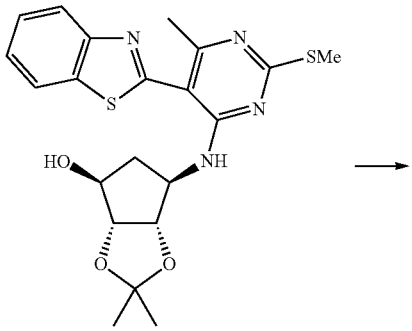
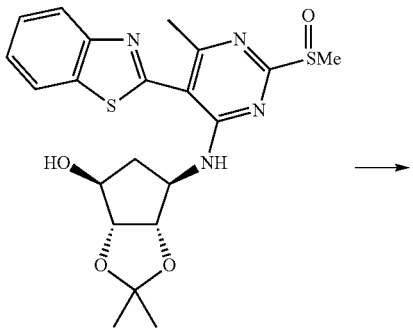


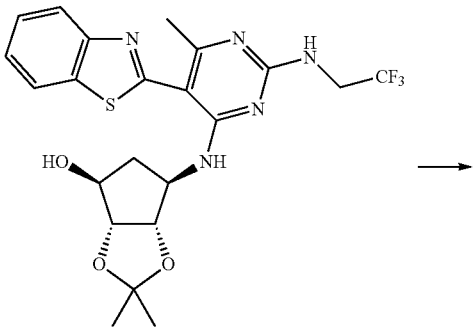
1366f



1366g



1366h



1366i

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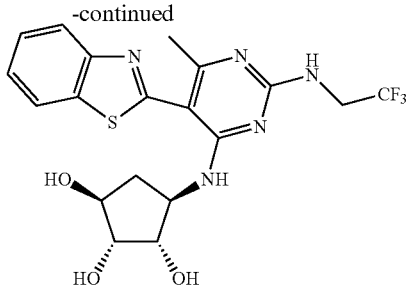


1366

Step 1:

Compound 1366a (429 mg, 3 mmol), potassium phthalimide (613 mg, 3.3 mmol), and Pd(PPh3)4 (300 mg) were dissolved in DMF (20 mL) and stirred at 90 C for 5 hours and then room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2:1 hexanes/ethyl acetate→1:1 hexanes/ethyl acetate) to provide compound 1366b (400 mg). [M+H]=212.11.

Step 2:

Compound 1366b (400 mg, 1.88 mmol) was dissolved in THF (20 mL) and water (2 mL) and treated with NMO (448 mg, 3.76 mmol) and osmium tetroxide (50 mg). After stirring for 12 hours the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was triturated with methylene chloride to provide 300 mg of compound 1366c.

Step 3:

Compound 1366c (300 mg, 1.13 mmol) was dissolved in acetone (15 mL) and 2,2-dimethoxypropane (1 mL) and treated with methanesulfonic acid (0.4 mL). After stirring for 3 hours the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide compound 1366d (300 mg). [M+H]=304.22

Step 4:

Compound 1366d (300 mg, 0.98 mmol) was dissolved in ethanol (5 mL) and treated with hydrazine monohydrate (0.5 mL). The reaction was stirred at 70 C for 2 hours. After cooling to rt, the solids were filtered and the filtrate was concentrated to provide 170 mg of compound 1366e. [M+H] =174.17

Step 5:

Reaction was performed in a similar manner to Procedure U, Step 1.

[M+H]=438.09

Step 6:

Reaction was performed in a similar manner to Procedure Z, Step 4.

[M+H]=445.20

Step 7:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=461.20

Step 8:

Reaction was performed in a similar manner to Procedure Z, Step 6.

[M+H]=496.11

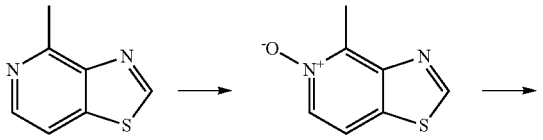
Step 9:

Reaction was performed in a similar manner to Procedure Z, Step 7.

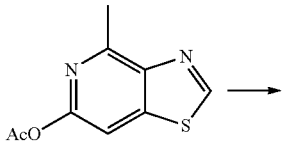
[M+H]=456

Example 1374

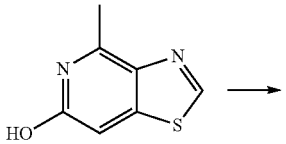
Procedure Z42



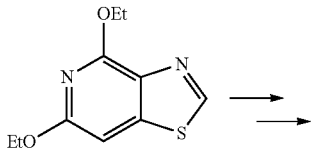
535c 1374a



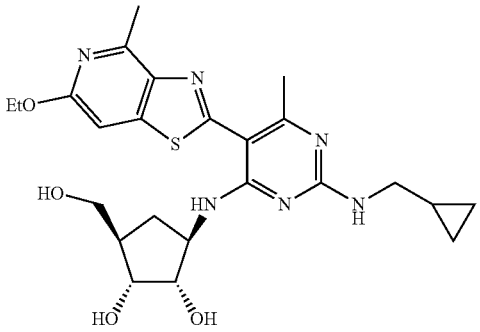
1374b



1374c



1374d



1374

Step 1:

Compound 535c (1.4 g, 9.27 mmol) was dissolved in methylene chloride (20 mL) and treated with 77% mCPBA (2.48 g, 11.1 mmol). After 2 hours the reaction was quenched with 1M potassium carbonate and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated to provide 1.2 g of compound 1374a.

Step 2:

Compound 1374a (1.2 g, 7.18 mmol) was dissolved in acetic anhydride (10 ml) and stirred at 120 C for 3 hours. The acetic anhydride was removed under reduced pressure and the residue was dissolved in ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide the desired product 1374b (300 mg). Also recovered 600 mg of the 6-membered rearrangement product.

Step 3:

Compound 1374b (300 mg, 1.44 mmol) was dissolved in 7M NH3 in methanol (5 mL) and stirred at rt for 2 hours. The solvent was removed under reduced pressure. The residue was triturated with diethyl ether to provide the desired product 1374c (150 mg). [M+H]=167.13

Step 4:

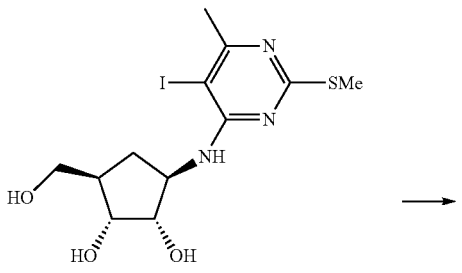
Compound 1374c (150 mg, 0.89 mmol) was dissolved in chloroform (15 mL) and treated with silver carbonate (0.5 g) and iodoethane (2 mL). The mixture was stirred at 90 C in a sealed vial. After 2 hours the reaction was filtered over celite and washed with water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide compound 1374d (125 mg). [M+H]=195.11

Step 5:

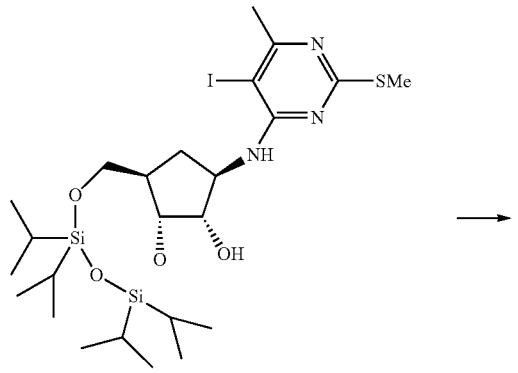
Compound 1374 was synthesized from 1374d using chemistry from Procedure Z.

Example 1383

Procedure Z43



329a



1383b

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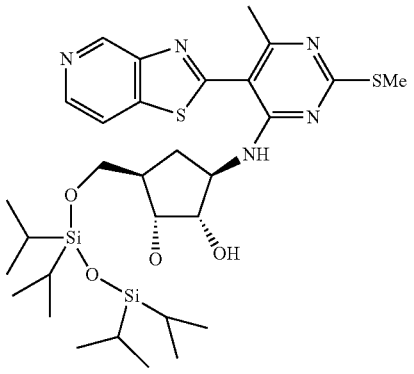
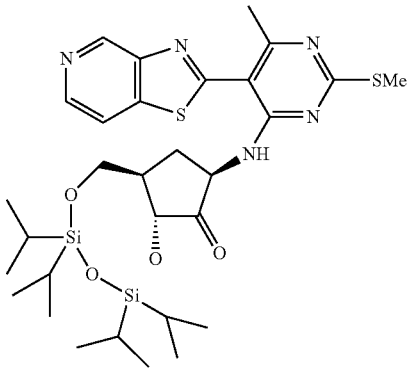
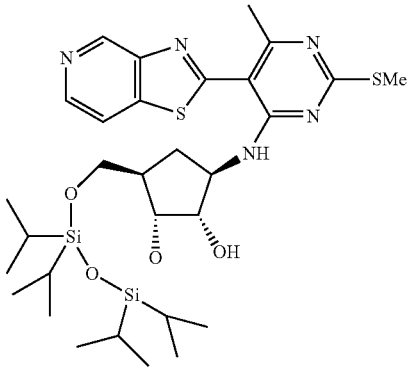


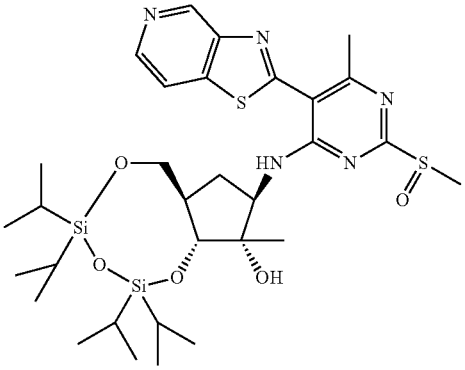
1383c



1383d



1383e



1383f

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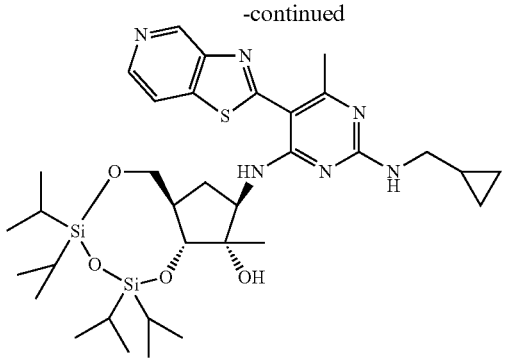
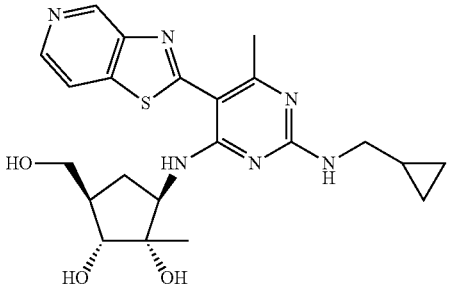


1383g



1383

Step 1:

Compound 329a (4.12 g, 10 mmol) was combined with imidazole (2.6 g, 40 mmol) and dissolved in DMF (40 mL). 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (3.3 mL, 10 mmol) was added dropwise in DMF (5 mL) and the reaction was stirred overnight. The reaction was quenched with water and extracted this ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (10:1 hexanes/ethyl acetate) to provide compound 1383b (6.0 g). [M+H]=654.6

Step 2:

Compound 1383c was synthesized from 1383b using Procedure Z, Step 4. [M+H]=662.46

Step 3:

Oxalyl chloride (103 mg, 0.82 mmol) was dissolved in methylene chloride (5 mL) and cooled to −78 C. DMSO (127 mg, 1.36 mmol) was added dropwise in methylene chloride (5 mL) and the reaction was stirred for 10 minutes. Compound 1383c (454 mg, 0.68 mmol) was dissolved in methylene chloride (5 mL) and added dropwise to the reaction mixture. After 15 minutes triethylamine (0.5 mL) was added and the reaction was slowly warmed to room temperature. After 2 hours the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (3:1 hexanes/ethyl acetate→1:1 hexanes/ethyl acetate) to provide compound 1383d (350 mg). [M+H]=660

Step 4:

Compound 1383d (200 mg, 0.303 mmol) was dissolved in THF (5 mL) and cooled to −78 C. A 3M solution of MeMgBr (0.3 mL, 9 mmol) was added dropwise and the reaction was stirred at −78 C for 1 hour and then slowly warmed to −30 C. After stirred for 3-4 hours the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over

sodium sulfate and concentrated. The residue was purified by column chromatography (3:1 hexanes/ethyl acetate→1:1 hexanes/ethyl acetate) to provide compound 1383e (120 mg) and recovered starting material (60 mg). [M+H]=676.44

Step 5:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=692.46

Step 6:

Reaction was performed in a similar manner to Procedure Z, Step 6.

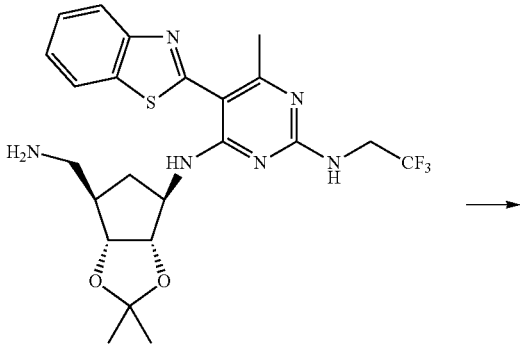
[M+H]=699.49

Step 7:

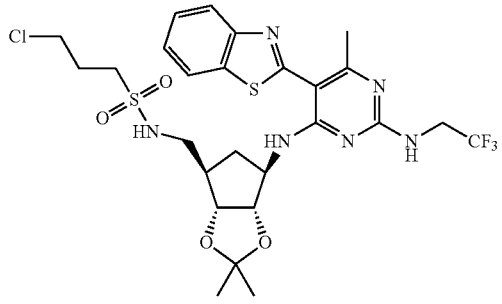
Compound 1383g (75 mg, 0.098 mmol) was dissolved in THF (5 mL) and treated with TBAF (26 mg, 0.098 mmol). After 2 hours the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (10:1 ethyl acetate/methanol) to provide the desired product 1383 (28 mg). [M+H]=457.30

Example 1396

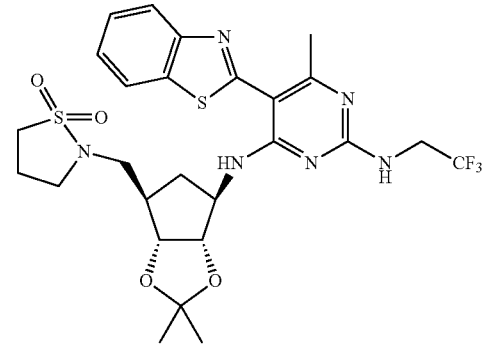
Procedure Z44



1396a

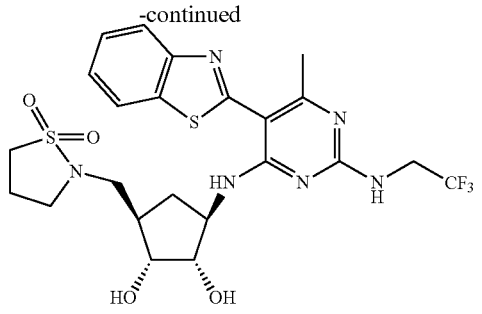


1396b



1396c

-continued



1396

Step 1:

Compound 1396a (60 mg, 0.118 mmol) was suspended in methylene chloride (8 mL) and triethylamine (0.041 mL, 0.295 mmol) and sonicated to make a solution. After cooling to 0 C, 3-chloropropane-1-sulfonyl chloride (25 mg, 0.14 mmol) was added dropwise in methylene chloride (2 mL). After stirring for 1 hour the reaction was quenched with water and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate 4 ethyl acetate) to provide product 1396b (65 mg). [M+H]=649.

Step 2:

Compound 1396b (65 mg, 0.1 mmol) was dissolved in DMF (5 mL) and treated with NaI (0.2 g) and cesium carbonate (0.5 g). The mixture was heated at 110 C for 1 hour and then quenched with water and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate 4 ethyl acetate) to provide product 1396c (60 mg). [M+H]=613.37

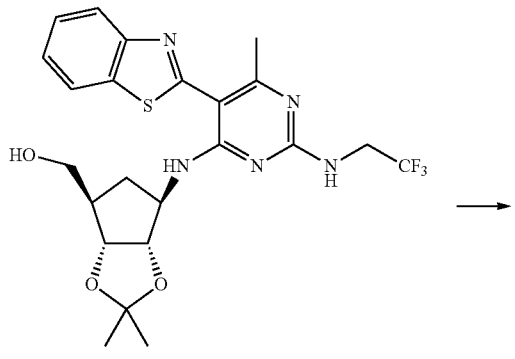
Step 3:

Reaction was performed in a similar manner to Procedure Z, Step 7.

[M+H]=573.29

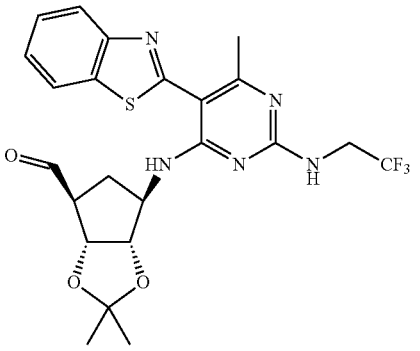
Example 1400

Procedure Z45



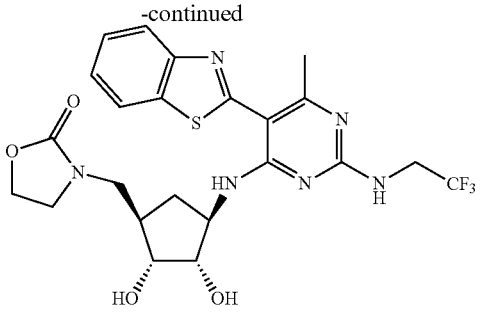
1015a

-continued



1015b

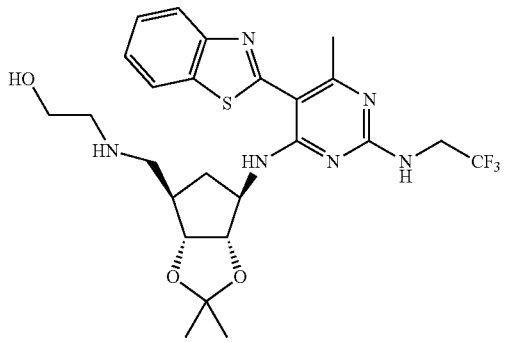
-continued



1400

Step 1:

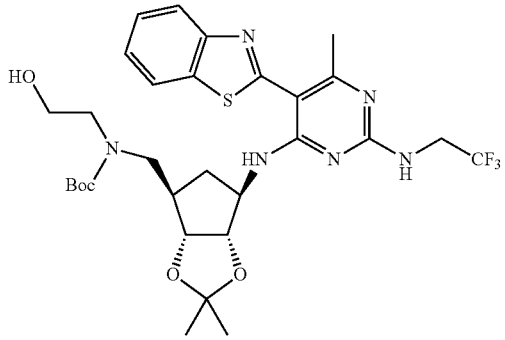
Compound 1015a (350 mg, 0.687 mmol) was dissolved in methylene chloride (10 mL) and cooled to 0 C. Dess Martin Periodinane (437 mg, 1.03 mmol) and a drop of water were added and the reaction was stirred for 3 hours and then quenched with sodium thiosulfate solution and saturated sodium bicarbonate. The mixture was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide 1015b (320 mg).



1400c

Step 2:

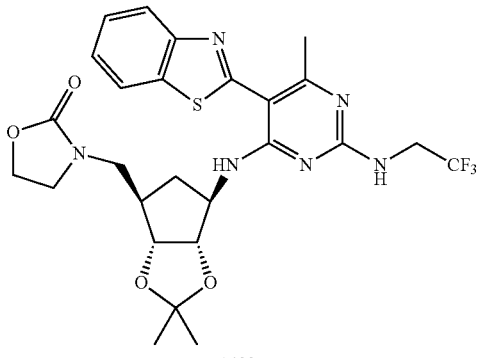
Compound 1015b (150 mg, 0.295 mmol) was dissolved in THF (5 mL) and treated with ethanolamine (72 mg, 1.18 mmol). The solution was stirred for 10 minutes and then sodiumtriacetoxyborohydride (0.6 g) was added and the reaction was stirred for 4 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide compound 1400c (160 mg). [M+H]=553



1400d

Step 3:

Compound 1400c (45 mg, 0.081 mmol) was dissolved in diethylcarbonate (1 mL) and treated with triethylamine (0.1 mL) and BOC2O (18 mg, 0.081 mmol). All were stirred at room temperature for 10 minutes and then 100 C for 6 hours. Removed solvent under reduced pressure and purified residue by column chromatography (1:1 hexanes/ethyl acetate) to provide compound 1400d (55 mg). [M+H]=653



1400e

Step 4

Compound 1400d (55 mg, 0.08 mmol) was dissolved in DMF (2 mL) and treated with 60% NaH (15 mg). The mixture was stirred at 100 C for 1 hour and then quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2:1 ethyl acetate/hexanes) to provide 1400e (25 mg).

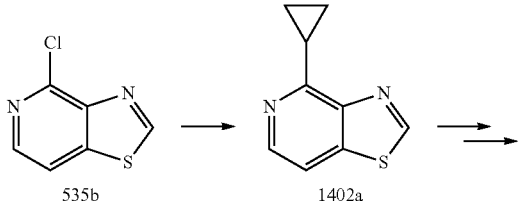
Step 5:

Reaction was performed in a similar manner to Procedure Z, Step 7.

[M+H]=539.33

Example 1402

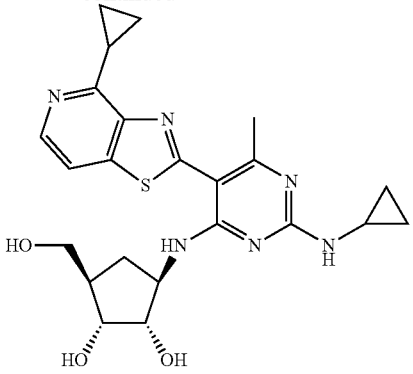
Procedure Z46



535b

1402a

-continued



1402

Step 1:

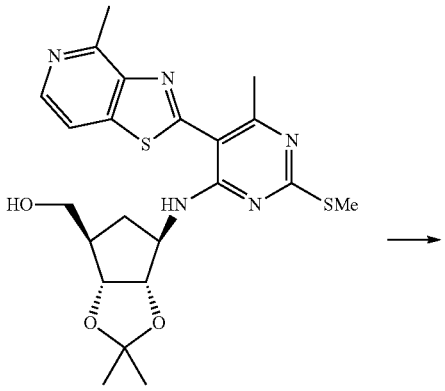
Compound 535b (200 mg, 1.17 mmol) and Pd(PPh3)4 (50 mg) were dissolved in 0.5M cyclopropylzinc bromide (4.6 mL, 2.33 mmol) and stirred at 70 C overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (2:1 hexanes/ethyl acetate) to provide 1402a (125 mg). [M+H]=177.11

Step 2:

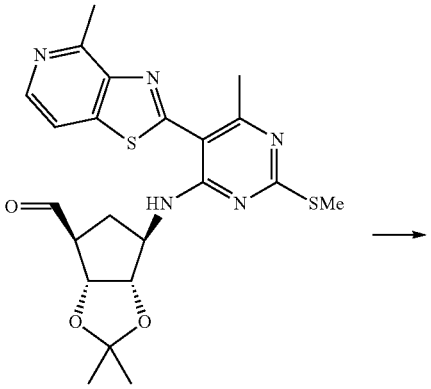
See procedure Z1 for similar experimental procedures.

Example 1398

Procedure Z47



535d



1398b

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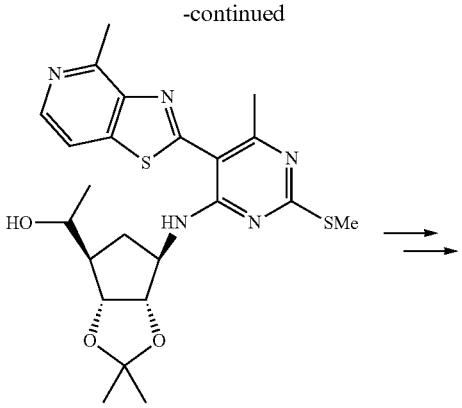
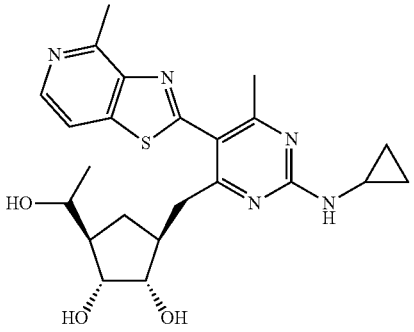


1398c



1398

Step 1:

Compound 535d (200 mg, 0.42 mmol) was dissolved in methylene chloride (20 mL) and 2 drops of water. Dess Martin Periodinane (356 mg, 0.84 mmol) was added at 0 C and the solution was stirred for 2 hours at 0 C and then overnight in a refrigerator. The reaction was quenched with quenched with sodium thiosulfate solution and saturated sodium bicarbonate. The mixture was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate) to provide 1398b (130 mg). [M+H]=472.25

Step 2:

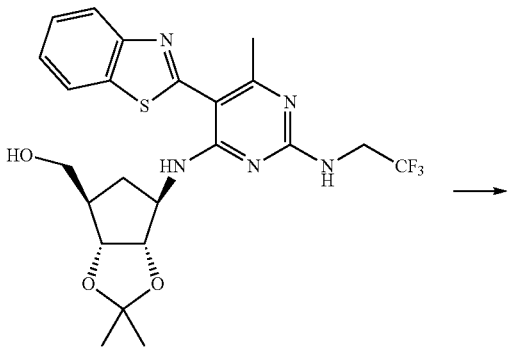
Compound 1398b (130 mg, 0.275 mmol) was dissolved in THF (5 mL) and cooled to 0 C. A solution of 3M MeMgBr in diethylether (0.91 mmol, 2.75 mmol) was added dropwise and the solution was stirred for 1 hr at 0 C and then quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate→10% MeOH) to provide compound 1398c (100 mg). [M+H]=488

Step 3:

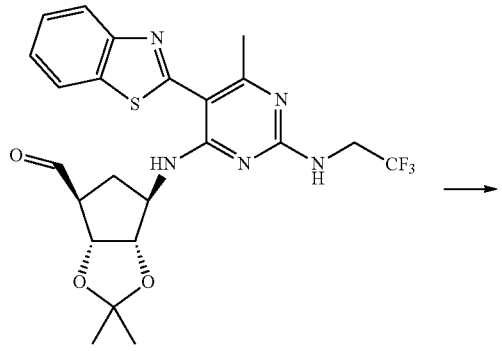
Compound 1398 was synthesized from 1398c using chemistry in Procedure Z1.

Examples 1392 and 1393

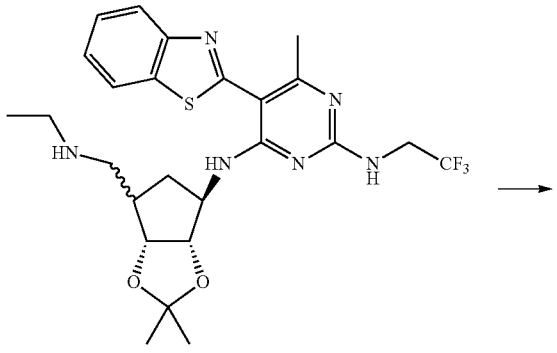
Procedure Z48



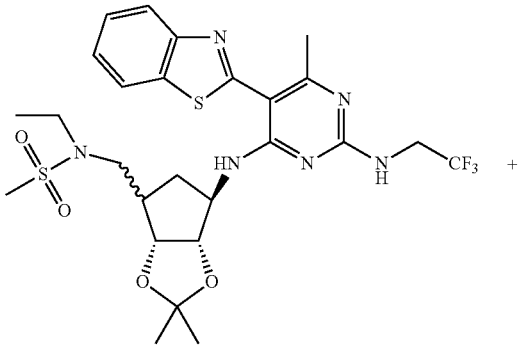
1015a



1392b

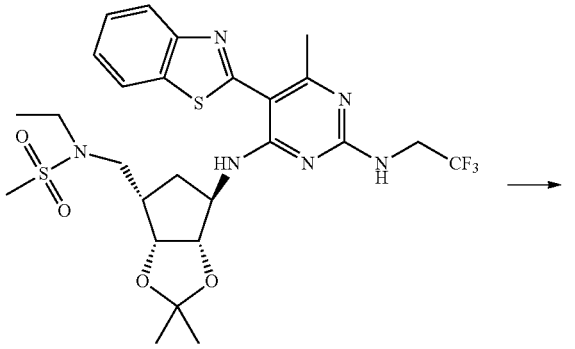


1392c

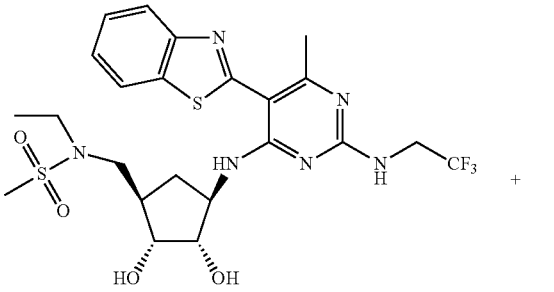


1392d

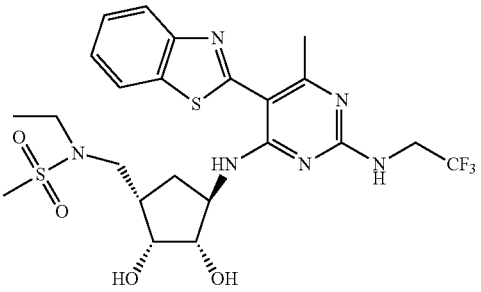
-continued



1393a



1392



1393

Step 1:

Compound 1015a (350 mg, 0.687 mmol) was dissolved in methylene chloride (10 mL) and cooled to 0 C. Dess Martin Periodinane (437 mg, 1.03 mmol) and a drop of water were added and the reaction was stirred for 3 hours at room temperature and then quenched with sodium thiosulfate solution and saturated sodium bicarbonate. The mixture was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide 1392b as a mixture of epimers (320 mg).

Step 2:

Compound 1392b (70 mg, 0.13 mmol) was dissolved in THF (5 mL) and treated with 2 Methylamine (0.138 mmol, 0.27 mmol). The solution was stirred for 10 minutes and then sodiumtriacetoxyborohydride (0.4 g) was added and the reaction was stirred for 4 hours. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated to provide compound 1392c (60 mg).

Step 3:

Compound 1392c (60 mg, 0.11 mmol) was dissolved in methylene chloride (5 mL) and triethylamine (0.1 mL) and cooled to 0 C. Methanesulfonyl chloride (13 mg, 0.11 mmol)

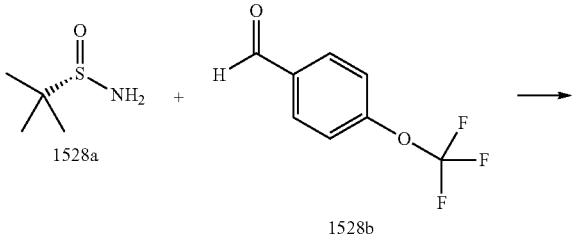
was added in methylene chloride (1 mL) dropwise. After 1 hour the reaction was quenched with water and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography to provide two products, compound 1392d (30 mg) and compound 1393a (30 mg).

Step 4:

The two compounds 1392 and 1393 were synthesized using Procedure Z, Step 7.

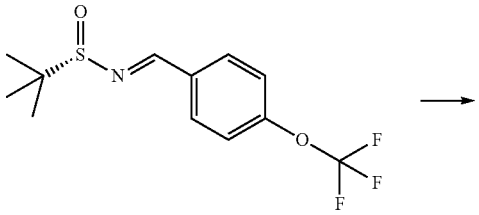
Example 1528

Procedure Z49

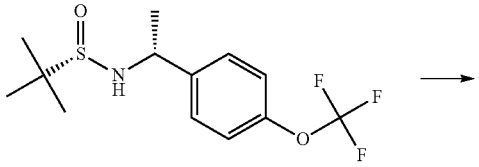


1528a

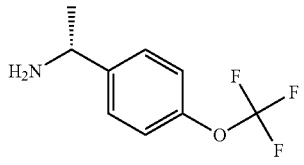
1528b



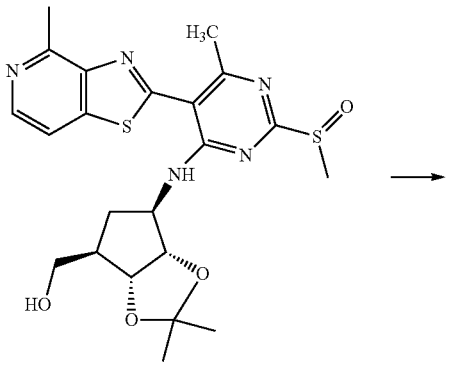
1528c



1528d



1528e



535e

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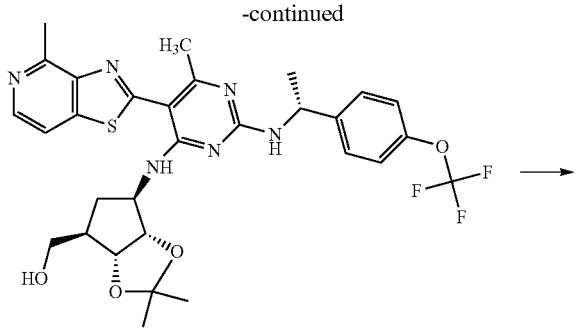
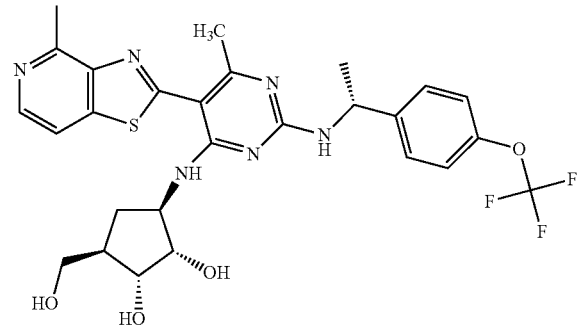


1528f



1528

Step 1:

Compound 1528a (2.54 g, 21.0393 mmol) and 1528b (4-(Trifluoromethoxy)benzaldehyde, 4.0 g, 21.0393 mmol) were stirred in 40.0 ml of THF and treated with Titanium isopropoxide (14.95 g, 15.7 ml, 52.598 mmol.). All were stirred at 70° C. for 6 h then allowed to stir at rt overnight. The reaction was diluted with water, then added ethyl acetate and filtered through a celite pad, rinsed with ethyl acetate. separate layers and extracted aqueous once more with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated to provide compound 1528c (4.85 g). [M+H]=294.16

Step 2:

Compound 1528c (4.85 g, 16.535 mmol) was dissolved in Anhydrous THF (104 ml) and cooled t-−30° to −40°. Added 3M (16.54 mL) of MeMgBr (dropwise) via an addition funnel. Stirred at −30° to −40° C. for 1 to 2 h. The reaction was monitored by TLC and MS [M+H]=310.21. The reaction was treated very slowly added with 150 mL of water at −45° C.−−50° C., then added 150 mL ethyl acetate, stirred and extracted 2-3 times, combined organics, dried over Na2SO4, filtered, concentrated, to obtain 1528d (3.51 g). [M+H]=310.28.

Step 3:

Compound 1528d (3.51 g, 11.34463 mmol) was stirred in anhydrous Methanol (30 ml) and at rt under N2, then added 4M HCl in 1-4 Dioxane (9.75 mL). Reaction was Allowed to stir for 2-3 hours at rt under N2. The reaction was monitored by TLC and MS [M+H]=206.14. Reaction was concentrated to dryness. An oily syrup residue obtain. Residue was treated with Diethyl Ether, stirred and a white solid formed. Mixture was filtered and white solid rinsed with ether. Isolated a white solid, dried under vacuum.

Afforded Compound 1528e (2.52 g). [M+H]=206.16. as an HCl Salt.

Step 4:

Compound 535e (620 mg, 1.2663 mmol) was dissolved in (3.5 mL) of 1,4-Dioxane art rt under N2, then added Compound 1528e (612 mg, 2.533 mmol) and (0.961 g, 1.324 ml, 9.497 mmol) of Triethylamine. Reaction mixture was heated to 120° C. The reaction was monitored by TLC and MS [M+H]=631.40. Reaction was concentrated to give a crude product. Purification by column chromatography (hexanes/Ethyl acetate→20% Methanol) to provide g of the product 1528f (0.575 g).

[M+H]=631.48.

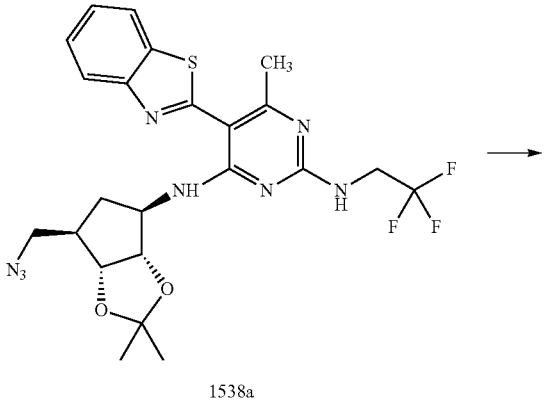
Step 5:

Compound 1528f (0.575 g, 0.9117 mmol) was stirred in Methanol (6.5 ml), followed by addition of 4M HCl in 1-4 Dioxane (3.5 ml) and water (0.3 mL). Allow reaction to stir at rt for 2-4 hours. Reaction monitored by MS [M+H]= 591.41. Concentrate rxn to dryness. a syrup obtain. Dry product under vacuum to obtain an ivory solid.

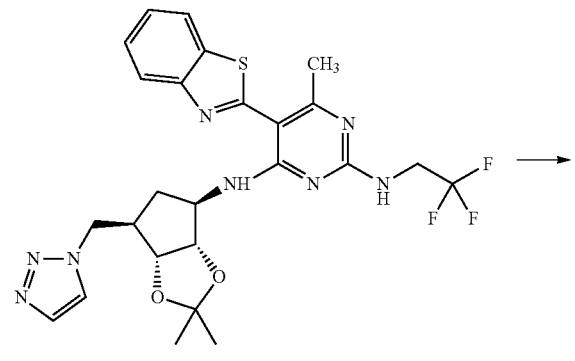
Afforded Compound 1528. (0.62 g) HCl Salt. LC MS [M+H]=591.2.

Example 1538

Procedure Z50

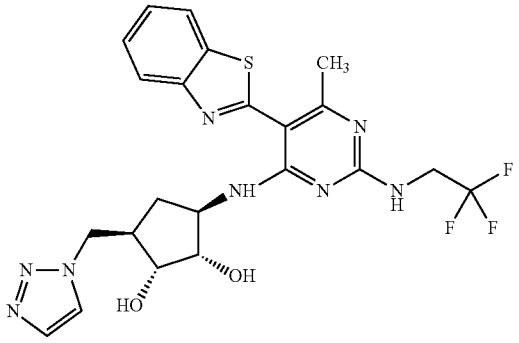


1538a



1538b

-continued



1538

Compound 1538a was synthesized using procedure Z34.

Step 1:

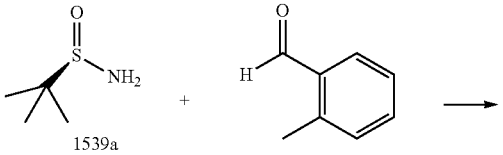
Compound 1538a (50 mg, 0.0935 mmol) and vinyl acetate (1 mL) were stirred in a pressure bottle at 120 C overnight. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over sodium sulfate, and concentrated to provide compound 1538b (33 mg). [M+H]= 560.59

Step 2:

1538 was synthesized from 1538b using procedure Z, Step 7.

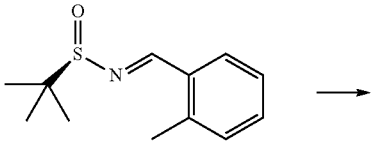
Example 1539

Procedure Z51

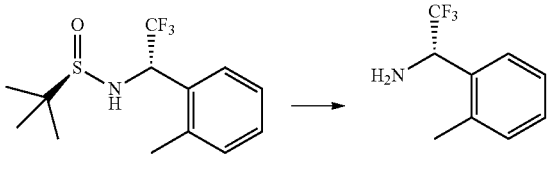


1539a

1539b



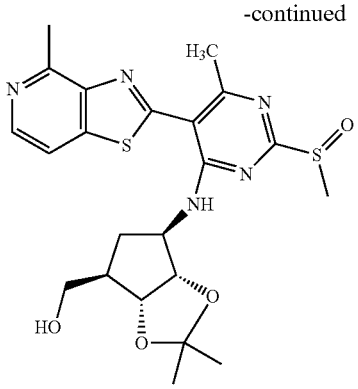
1539c



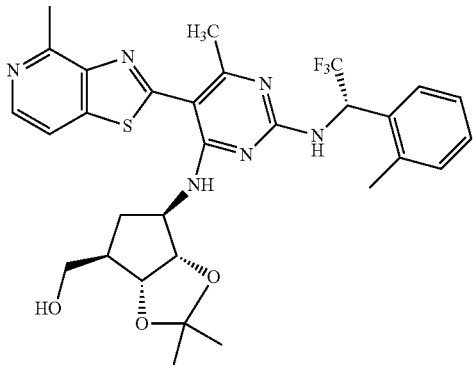
1539d

1539e

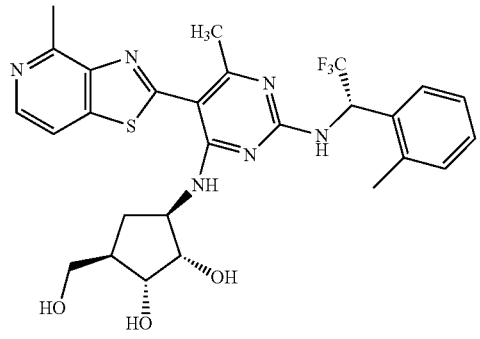
-continued



535e



1539f



1539

Step 1: Compound 1539c was synthesized from 1539a and 1539b using Procedure Z49.

Step 2:

Combined in a flame-dried round-bottom flask Compound 1539c (0.6 g, 2.687 mmol) and Tetrabutyl ammonium difluorotriphenylsilicate (2.176 g, 4.0305 mmol) and dissolved and stir in Anhydrous THF (13.3 ml); and cooled t--78° C., then Added TMS-CF3 (0.573 g, 0.595 ml, 4.0305 mmol.) in 13.3 ml of anhydrous THF) (dropwise) via an addition funnel for a period of 10 minutes. Then allow to stir for 2 hours at 0 degrees C. Quench reaction mixture at 0 degrees C. with saturated Ammonium Chloride; Extracted ethyl acetate 2-3 times, combined organics, dried over Na2SO4, filtered, concentrated, to obtain crude product. [M+H]=294.25. Purification by column chromatography afforded 1539d (0.46 g). [M+H]=294.19.

Step 3:

Compound 1539d (0.46 g, 1.568 mmol) was stirred in anhydrous Methanol (3 ml) and at rt under N2, then added 4M HCl in 1-4 Dioxane (1.0 mL). Reaction was Allowed to stir for 2-3 hours at rt under N2. The reaction was monitored by TLC and MS [M+H]=190.14. Reaction was concentrated to dryness. An oily residue obtain. Residue was treated with ethyl acetate (1 ml) and Diethyl Ether (5 ml), stirred and a white solid formed. Mixture was filtered and white solid rinsed with ether. Isolated a white solid, dried under vacuum. Afforded Compound 1539e (0.3 g) as an HCl Salt. [M+H]=206.16.

Step 4:

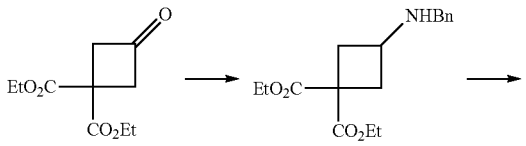
Compound 535e (50 mg, 0.102 mmol) was dissolved in (1.0 mL) of 1,4-Dioxane art rt under N2, then added Compound 1539e (159 mg, 0.71 mmol) and (0.132 ml, 1.02 mmol) of diipropylethylamine. Reaction mixture was heated to 130° C. The reaction was monitored by TLC and MS [M+H]=615.42. Reaction was concentrated to give a crude product. Purification by column chromatography (hexanes/Ethyl acetate→45% Methanol) to provide g of the product 1539f (26.9 mg). [M+H]=631.48.

Step 5:

Compound 1539f 23 mg, 0.0374 mmol) was stirred in Methanol (3.0 ml), followed by addition of 4M HCl in 1-4 Dioxane (1 ml) and water (0.2 mL). Allow reaction to stir at rt for 2-4 hours. Reaction monitored by MS [M+H]=575.39. Concentrate r×n to dryness. Dried product under vacuum to obtain an ivory solid. Afforded Compound 1539. (0.24 mg) HCl Salt. LC MS [M+H]=575.39.

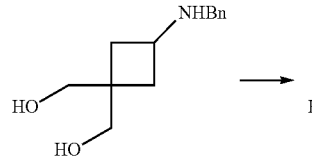
Example 1610

Procedure Z56

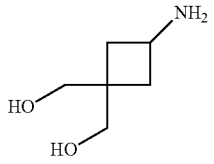


1610a

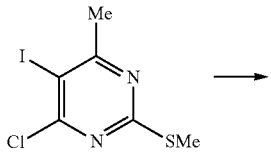
1610b



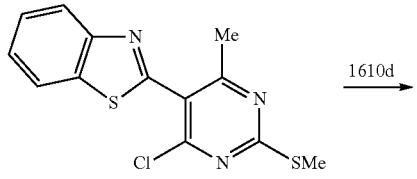
1610c



1610d



324d



1610e

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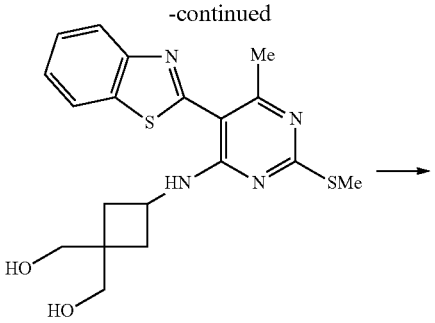
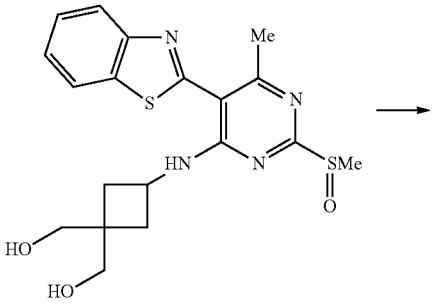
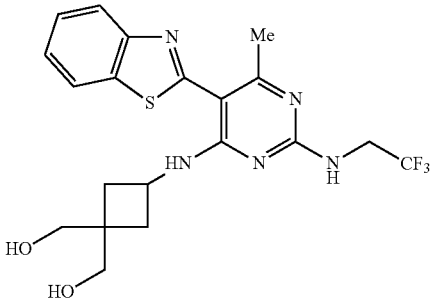


1610f



1610g



1610

The ketone (569 mg, 1610a) was dissolved in DCE (9 mL), followed by the addition of benzyl amine (290 uL) and the borohydride (788 mg). The reaction was allowed to stir at rt for 45 min—MS indicated reaction was complete, as did TLC. Quench with 50 mL NaHCO3 and extract 3×50 mL EtOAc, dry over MgSO4, filter and concentrate. Obtained 690 mg of 1610b.

Diester 1610b (from above) was dissolved in THF (6 mL), followed by the addition of LiBH4 (2M/THF, 1.2 mL) at rt. Reaction allowed to stir at rt, overnight. Reaction complete by TLC and MS. Quench with 10 mL NH4Cl and allowed to stir at rt for 1 h. Dilute with 20 mL H2O and extracted 3×30 mL EtOAc and concentrated. Flash chromatography—1 to 10% MeOH/DCM—isolated 96.2 mg of 1610c (69%).

1610c (from above) was dissolved in MeOH (3 mL), and a catalytic amount of $Pd(OH)_2$ added. Purged 5× with H2 and put under 1 atm H2 and let stir at rt overnight. Reaction complete by MS. Filter over celite and concentrate. Obtained 57.5 mg of 1610d.

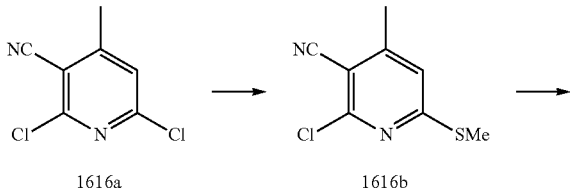
Conversion of 324d to 1610e. Performed as in procedure U.

Conversion of 1610e to 1610f. Performed as in procedure U.

Conversion of 1610f to 1610g and then to required product 1610. Performed as in procedure Z.

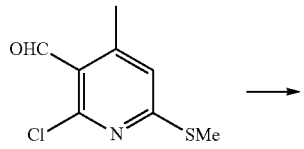
Example 1616

Procedure Z57

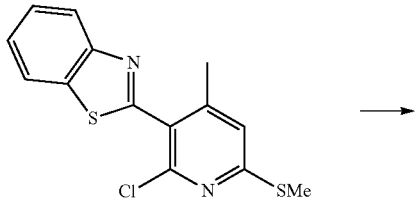


1616a

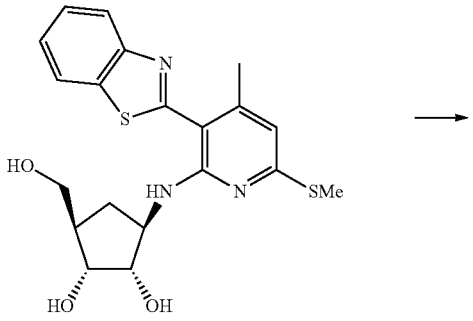
1616b



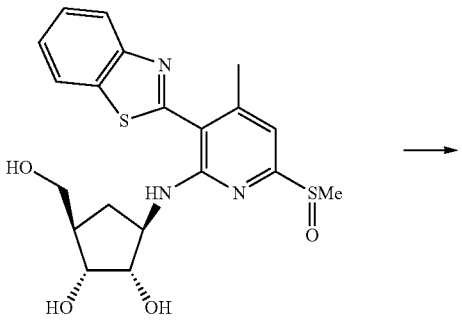
1616c



1616d



1616e



1616f

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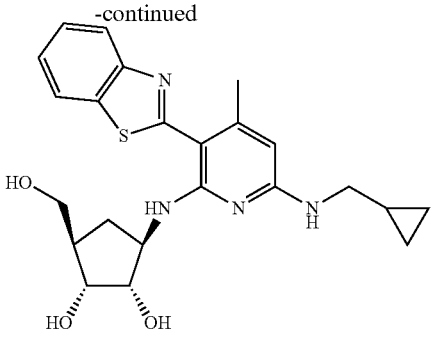


1616

Step 1: SM, 1616a (4.8 g) dissolved in THF (100 mL). NaSMe (2 g), followed immediately by CuBr (220 mg) was added and reaction heated from rt to 60° C. for 5 h. Quench with 100 mL NaHCO3 and 100 mL H_2O and extract 3×100 mL EtOAc and concentrate. Flash chromatography -1 to 5% EtOAc/hexanes to 1 to 5% EtOAc/DCM. 3.06 g of desired, 1616b (61%) and 998 mg of undesired regioisomer obtained.

Step 2: 1616b (694 mg) dissolved in CH_2Cl_2 (20 mL) and cooled to −78° C. DIBAL (1M/hexanes, 3.8 mL) added dropwise over 1 min and let stir at −78° C. for 2 h. then warmed to rt. After 15 min quench with 30 mL NH_4Cl and acidify with 30 mL 3N HCl. Extract 3×40 mL EtOAc, dry over $MgSO_4$, filter and concentrate. Flash chromatography—5 to 15 to 20% EtOAc/hexanes, gave 459.8 mg of 1616c (65%).

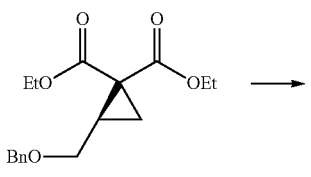
Step 3: Aminothiophenol (100 uL) added to aldehyde 1616c (156 mg) dissolved in MeOH/DMF (5/0.5 mL), followed by AcOH (100 uL) and let stir overnight. Reaction complete to the thiazoline by MS and LCMS. H2O added to the reaction and filtered through a glass frit. Washed 5× with H2O, then dissolved in CDCl3 and 262.2 mg DDQ added and let stir at rt. Reaction complete within 10 min. Add 20 mL 10% K2CO3 and extract 2×40 mL CHCl3, dry over MgSO4, filter and concentrate to give 1616d.

Step 4: 1616d, (178 mg) dissolved in NMP (2 mL) in a microwave vial and carbasugar, 120a (323 mg) followed by DBU (350 uL) added. Microwave for 30 min at 200° C. Reaction complete by MS. Dilute with 40 mL H2O and extract 2×30 mL EtOAc and concentrate. Dissolve in DCM, gave lots of insoluble material. Filter through a frit funnel—MS and NMR indicates solid is clean product. Take filtrate and concentrate. Redissolve in DCM and filter. Combined solid material to give 1616e, 94.1 mg (39%).

Step 5 & 6: Conversion of 1616e to 1616f and further to 1616, as in procedure Z.

Example 1617

Procedure Z58



1617a

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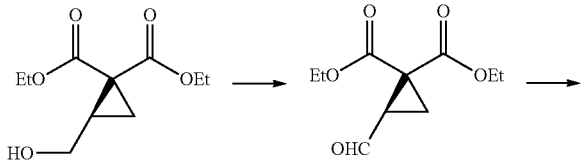
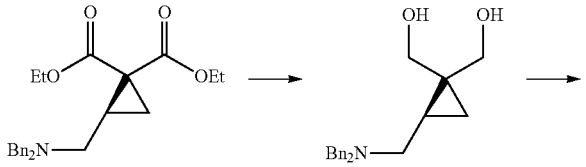


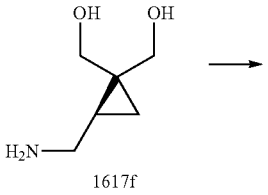
1617b

1617c

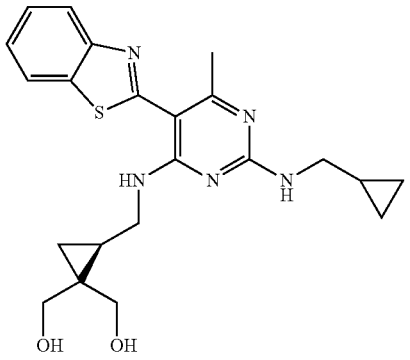


1617d

1617e



1617f



1617

1617a was synthesized by the method of: Burgess, K.; Ye, C-Y. *Synthesis* 1996, 1463.

Step 1: Hydrogenation of 1617a to give 1617b, as in procedure Z56.

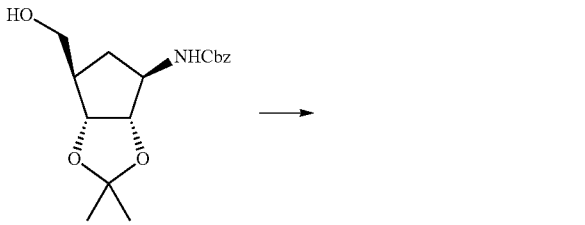
Step 2: 1617b, (538 mg) dissolved in CH2Cl2 (3 mL). NaHCO3 (660 mg), then Dess-Martin's periodinane (2 g) was added and let stir at rt. Add 4 mL (total of 7 mL) CH_2Cl_2 and let stir. After 45 min, TLC indicates reaction is complete. Quench with 5 mL 1M Na2S2O3 and let stir till organic layer is clear. Dilute with 20 mL H_2O and extract with 3×30 mL EtOac, dry over $MgSO_4$, filter and concentrate. Obtained 506.6 mg of 1617c, 95%.

Steps 3, 4 & 5: As in procedure Z56.

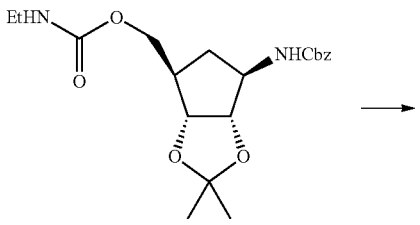
Step 6: Conversion of 1617f to 1617, as in procedure Z.

Example 1628

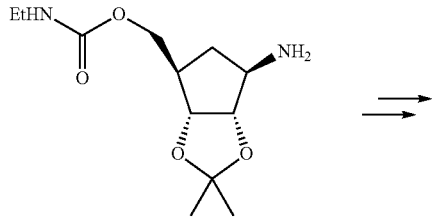
Procedure Z59



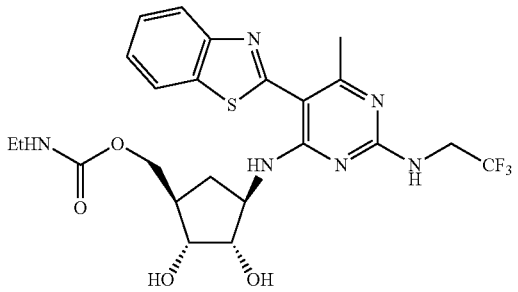
120c



1628c



1628d



1628

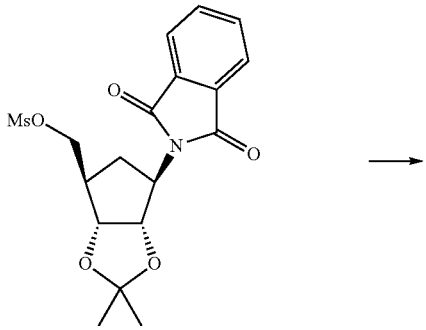
Step 1: SM, 120c (630 mg) dissolved in DMF (13 mL), then ethylisocyanate (170 mg) followed by CuCl (160 mg) added to flask. Let stir at RT, overnight. 80 mg isocyanate and 79.0 mg CuCl were added. Heated to 60° C. Stopped reaction and purified via flash chromatography to give 69.8 mg of 1628c.

Step 4: 1628c (70 mg) dissolved in EtOH (5 mL) and scoop of 10% Pd/C added. Fitted with a H2 balloon and flushed 5×, then let stir at rt for 2 h. Complete by MS. Filter over celite and concentrate to give 46.0 mg of 1628d.

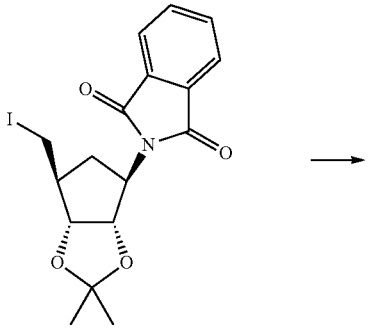
Conversion of 1628d to 1628, as in procedures U & Z.

Example 1630

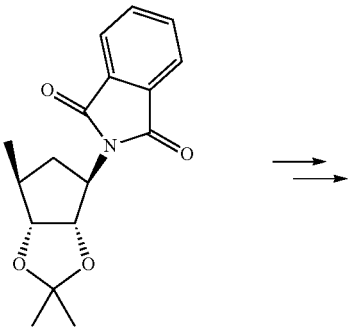
Procedure Z60



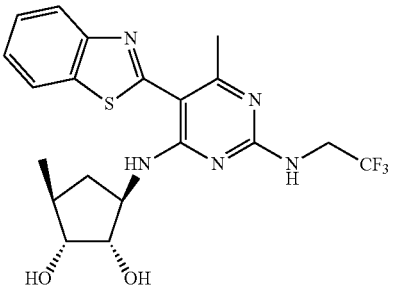
1367b



1630b



1630c



1630

Step 1: SM, 1367b (20 mg) dissolved in acetone (300 uL) and NaI (75 mg) added. Let stir at rt for 2 h. Heated to 50° C. Reaction essentially complete by TLC. Dilute with 1 mL

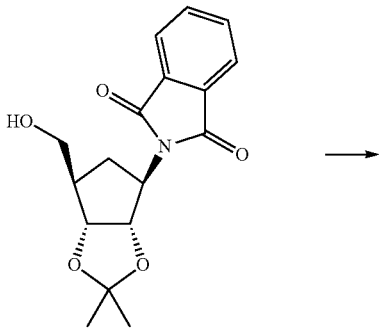
H2O and extract 2×2 mL EtOAc, dry over MgSO4, filter and concentrate. Isolated 18.7 mg of 1630b (88% crude yield).

Step 2: SM, 1630b (19 mg) dissolved in EtOH (1.5 mL). Et3N (15 uL) added, followed by scoop of 10% Pd/C. Hydrogenated with a balloon of H2, flushed 5×, and let stir overnight. Filter over celite and concentrate. 18.4 mg of 1630c was isolated.

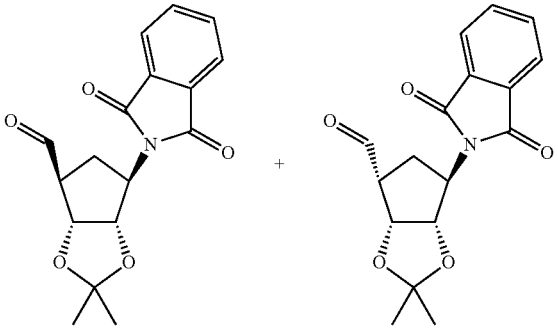
Conversion of 1630c to 1630, as in Z40 and Z56.

Example 1632

Procedure Z61

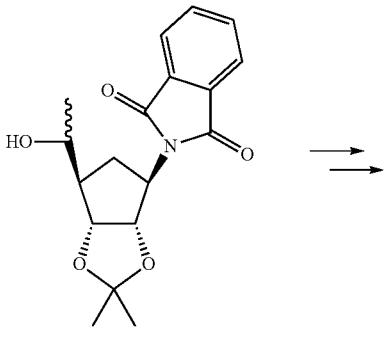


1350a



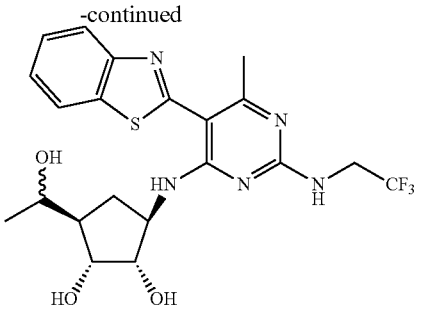
1632a + 1632b

1632a →



1632c

-continued



1632

Step 1: $(COCl)_2$ (1 mL) dissolved in 30 mL DCM and cooled to −78° C. DMSO (1.8 mL) added dropwise and let stir 10 min. SM, 1350a (2.2 g) added in 20 mL DCM. Stir for 1 h. Et3N added and let stir at rt. Quench after 2 h with 60 mL H2O and diluted with 250 mL DCM. Organic layer washed with H2O (60 mL), NH4Cl (2×60 mL), NaHCO3, (60 mL) and brine (60 mL). Organic layer dried over MgSO4, filtered and concentrated. Flash chromatography—10 to 60% EtOAc/hexanes gave 1.71 g of product—NMR indicates approximately 1:1 ratio of epimerized aldehydes. Flash chromatography—EtOAc/DCM/hexanes resulted in separate isomers, 1632a and 1632b.

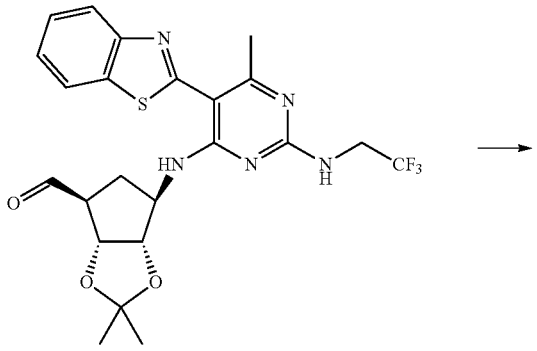
Step 2: SM, 1632a (100 mg) dissolved in THF and cooled to −78° C. MeMgBr (3M, 110 uL) added dropwise and let stir at −78° C. for 1 h. Reaction complete by TLC. Quench with 5 mL NH4Cl and let stir at rt. Dilute with 25 mL H2O and extract 2×35 mL EtOAc, dry over MgSO4, filter and concentrate. Flash chromatography -30 to 60% EtOAc/hexanes gave 60.6 mg of a ~1:1 mixture of diastereomers, 1632c (57%).

Remaining Steps:

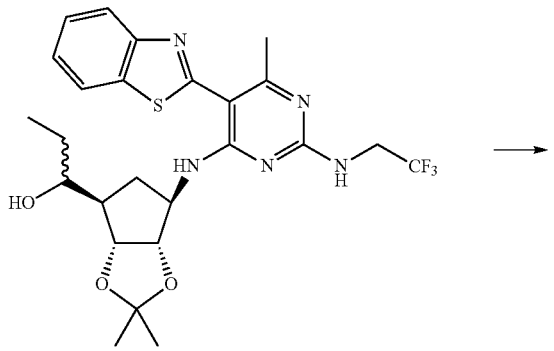
Conversion of 1632c to 1632, as in Z40.

Example 1637

Procedure Z62

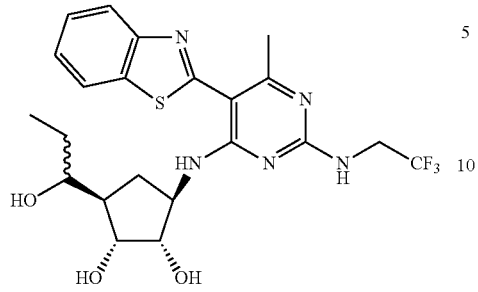


1015b



1637a

-continued



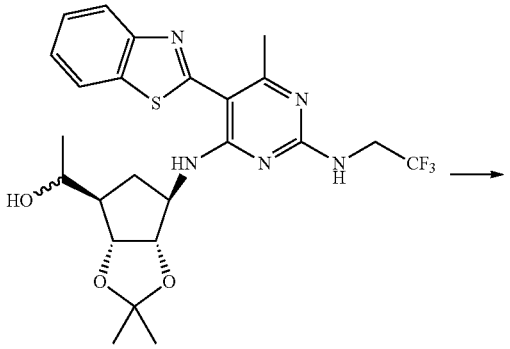
1637

Step 1: SM, 1015b (48 mg) dissolved in THF (3 mL) and cooled to −78° C. EtMgBr (3M, 100 uL) added dropwise and let stir at −78° C. for 2 h. One eq of EtMgBr added. Almost complete by TLC and MS. After 2 h, quench with 5 mL NH4Cl and let stir at rt. Dilute with 25 mL H2O and extract 3×30 mL EtOAc, dry over Na2SO4, filter and concentrate. Flash chromatography −5 to 50% EtOAc/hexanes gave 23.7 mg of 1637a (44%).

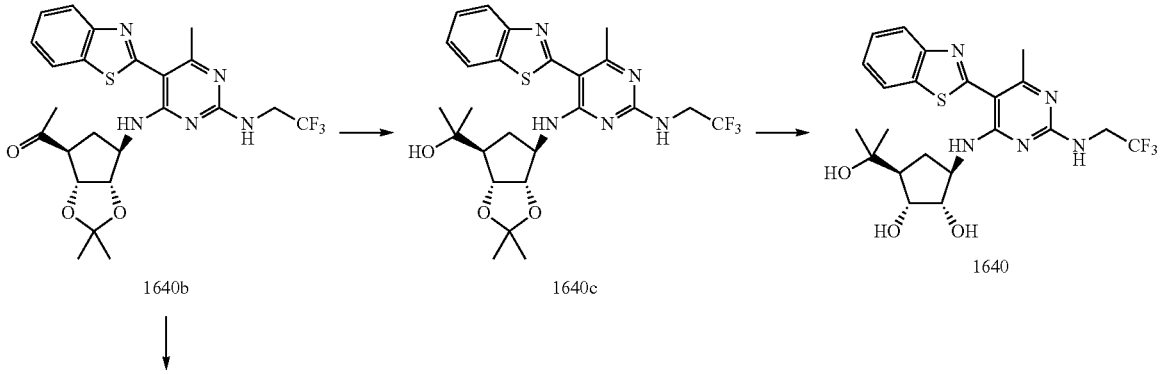
Step 2: Conversion of 1637a to 1637, as in procedure Z.

Examples 1636 and 1640

Procedure Z63



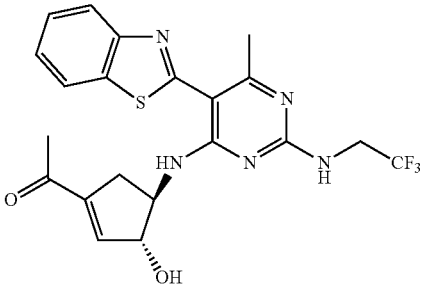
1640a



1640b

1640c

1640



1636

Step 1: SM, 1640a (102 mg, obtained as in procedure Z62, step 1) dissolved in CH_2Cl_2 (4 mL). NaHCO3 (51 mg), then Dess-Martin's periodinane (164 mg) added and let stir at rt for 4.5 h. TLC and MS indicates reaction is complete. Quench with 5 mL 10% Na2S2O3 and let stir till organic layer is clear. Dilute 20 mL H2O and extract 3×30 mL EtOac, dry over MgSO4, filter and concentrate. Obtained 110.0 mg of 1640b.

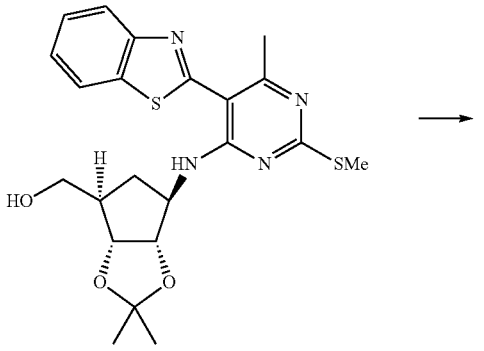
Step 2: Conversion of 1640b to 1640c, as in procedure Z62.

Remaining Steps:

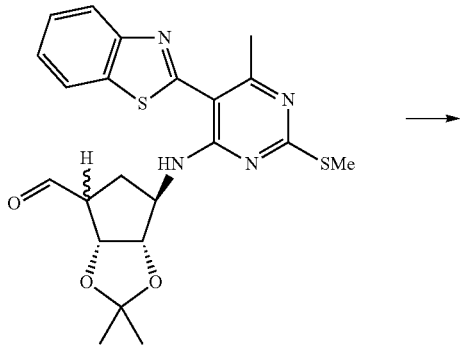
Conversion of 1640b to 1636, and 1640c to 1640, as in procedure Z, with modifications.

Example 1643

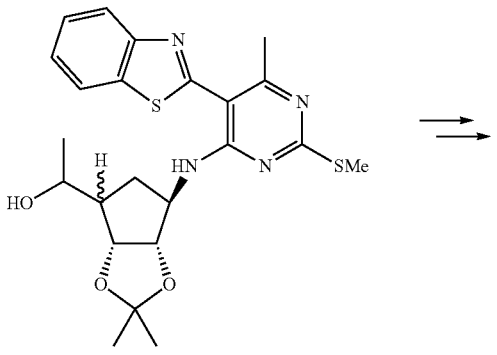
Procedure Z64



329d

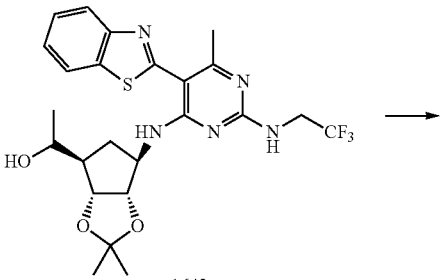


1643a



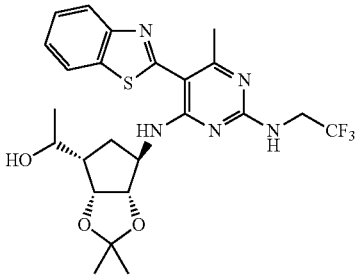
1643b

-continued

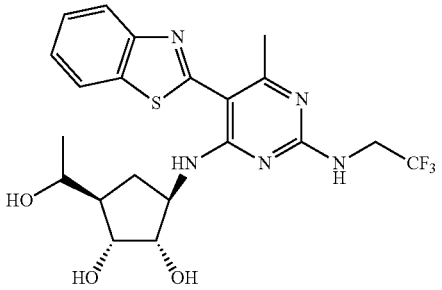


1643c

+



1643d



1643

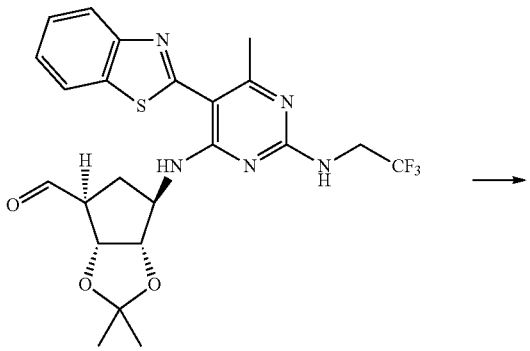
Step 1: SM, 329d (2.2 g) dissolved in CH_2Cl_2 (40 mL), cooled to 0° C., then Dess-Martin's periodinane (DMP, 2.5 g) added and let stir at rt 3 h. Add 2.5 g DMP. After 30 min, complete by TLC. Quench with 25 mL 10% Na2S2O3 and let stir till organic layer is clear. Dilute 100 mL H2O and extract 3×80 mL EtOac, dry over Na2SO4, filter and concentrate to give 2.66 g of 1643a.

Step 2: SM, 1643a (390 mg) dissolved in THF (20 mL) and cooled to −78° C. MeMgBr (3M, 1.7 mL) added dropwise and let stir at −78° C. for 2 h. Quench with 20 mL NH4Cl and let stir at rt. Dilute with 75 mL H2O and extract 3×50 mL EtOAc, dry over Na2SO4, filter and concentrate. Flash 20 to 40% EtOAc/hexanes to give 1643b (102.3 mg of isomer 1 and 151.2 mg of isomer 2 at the newly created stereocenter).

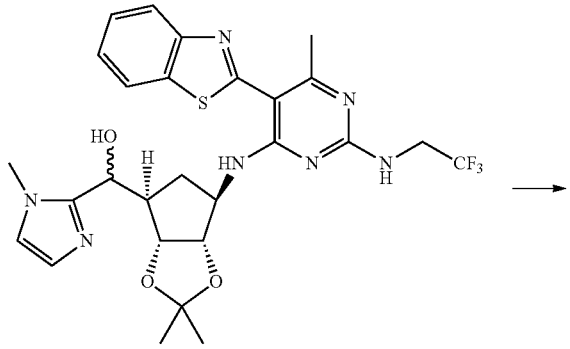
Remaining steps: As in procedure Z (single isomers 1643c and 1643d were separated at amine displacement of sulfoxide stage). 1643c was carried forward to 1643.

Example 1653

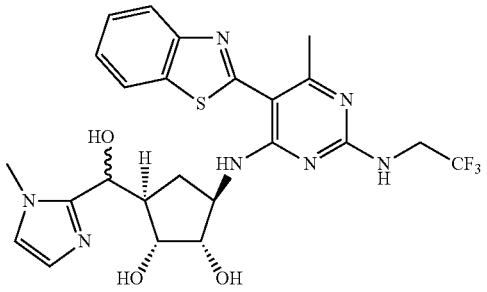
Procedure Z66



1015b



1653a



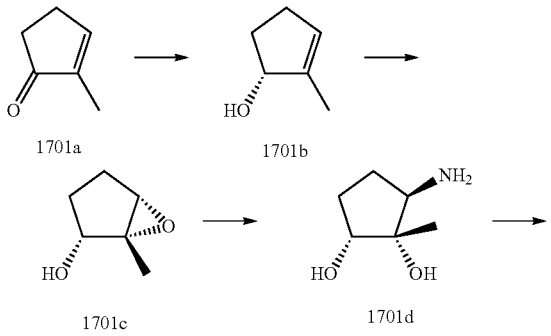
1653

Step 1: Imidazole (17 uL) dissolved in THF (2 mL) and cooled to −78° C. n-BuLi (1.6M, 130 uL) added and let stir 15 min, then aldehyde, 1015b (0.2 mmol) added. After 30 min, add 10 eq. imidazole/n-BuLi mixture (pre-formed at rt) to reaction. Quench with 10 mLNH4Cl, dilute with 50 mL H2O and extract 2×50 mL EtOAc. Dry Na2SO4, filter and concentrate. Flash chromatography gave 49.0 mg of 1653a.

Step 2: Conversion of 1653a to 1653, as in procedure Z.

Example 1701

Procedure Z67

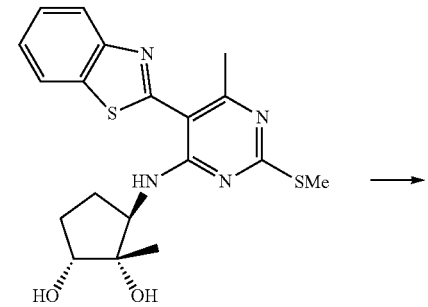


1701a

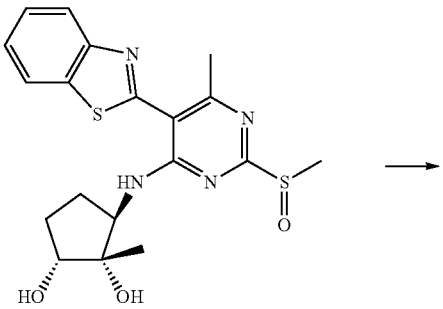
1701b

1701c

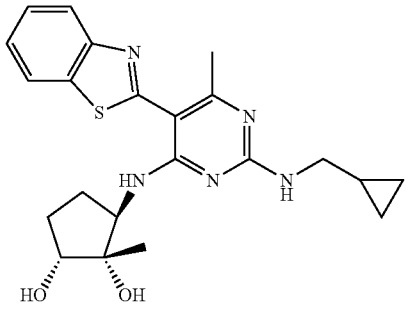
1701d



1701e



1701f



1701

Step 1:

A solution of 2-methyl-cyclohex-2-en-1-one (1701a) (4.0 g, 41.61 mmol, 4.08 mL, d 0.979) in dry dichloromethane (80 mL) was slowly added (over 30 min) to an ice-cooled solution of (R)-1-methyl-3,3-diphenylhexahydropyrrolo[1,2-c][1,3,2]oxazaborole (Corey's Me-CBS, 10 mol %, 4.2 mL of 1 M solution in toluene) and borane-dimethylsulfide

complex (1.0 eq, 4.16 mL) in dichloromethane (20 mL). After addition was completed the mixture was stirred for further 15 min. The reaction was quenched by careful and slow addition of methanol (20 mL). The mixture was concentrated in rotavap and the residue was diluted with aqueous saturated sodium bicarbonate (100 mL), the product was extracted into ethyl acetate (4×100 mL). The combined organic extracts were washed with aqueous saturated sodium bicarbonate (50 mL), aqueous saturated ammonium chloride (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Redisep (120 g) silica gel column (gradient: 0 to 50% ethyl acetate in hexanes) to give the product 1701b (2.7 g, 67%) as a colorless oil.

Step 2:

A solution of (R)-2-methylcyclopent-2-enol (1701b) (300 mg, 3.056 mmol) in 30 mL of benzene was cooled in an ice-water bath and treated with $VO(acac)_2$ (5 mol %, 219 mg) and tert-butylhydroperoxide (1.0 eq, 2.13 mL of 70 wt % in water). The reaction mixture was stirred for 10 min and a second equivalent of t-butylhydroperoxide was added. The reaction was stirred for further 20 min at room temp. The mixture was cooled again and a third equivalent of t-butylhydroperoxide was added. The reaction was stirred for further 20 min at room temp and TLC (30% ethyl acetate in hexanes) showed complete conversion. The mixture was treated with aqueous 10% sodium thiosulfate (50 mL) and vigorously stirred for 10 min. The product was extracted into ethyl acetate (1×100 mL, 2×50 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Redisep (120 g) silica gel column (0 to 70% ethyl acetate in hexanes) to give the product 1701c (1.0 g, 54%) as a colorless oil.

Step 3:

A microwave reaction tube was charged with a solution of (1R,2R,5S)-1-methyl-6-oxabicyclo[3.1.0]hexan-2-ol (1701c) (90 mg, 0.788 mmol) in 1 mL of dioxane. Concentrated ammonium hydroxide was added (2 mL) and the tube was sealed. The reaction was carried out in microwave at 135° C. for 30 min. TLC (50% ethyl acetate in hexanes) showed complete conversion. The mixture was concentrated in rotavap and the residual water was co-evaporated with benzene to give the crude product 1701d (ca 99%, 102 mg) as a slightly yellow oil.

Step 4:

A solution of (1S,2R,5R)-5-amino-1-methylcyclopentane-1,2-diol (1701d) (1.1 eq, 117 mg) in ethanol (8 mL) was treated with 2-(4-chloro-6-methyl-2-(methylthio)pyrimidin-5-yl)benzo[d]thiazole (250 mg, 0.812 mmol) and triethylamine (4.0 eq, 0.456 mL, d 0.720). The mixture was heated in an oil bath at 80° C. for 20 h. LCMS showed partial conversion (approx 20% SM left). All the volatiles were removed in rotavap and the residue was dried under vacuum. The crude product was purified on a Redisep (24 g) silica gel column (gradient: 0 to 40% ethyl acetate in dichloromethane) to give the product 1701e (214 mg, 60%) as a white solid.

Step 5:

A solution of (1S,2R,5R)-5-(5-(benzo[d]thiazol-2-yl)-6-methyl-2-(methylthio)-pyrimidin-4-ylamino)-1-methylcyclopentane-1,2-diol (1701e) (200 mg, 0.496 mmol) in 10 mL of dichloromethane was placed in an ice-water bath and treated with m-CPBA (1.3 eq, 148 mg of 75% m-CPBA). The reaction mixture was stirred for 5 min and TLC (30% ethyl acetate in dichloromethane) showed complete consumption of the starting material. The reaction was treated with aqueous saturated sodium bicarbonate soln (10 mL) and the product was taken into ethyl acetate (50 mL). The layers were separated and the organic layer was washed with aqueous saturated sodium thiosulfate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to give the crude product 1701f (207 mg, 100%) as a white solid which was used without further purification. LCMS showed 80:20 distribution between sulfoxide/sulfone products.

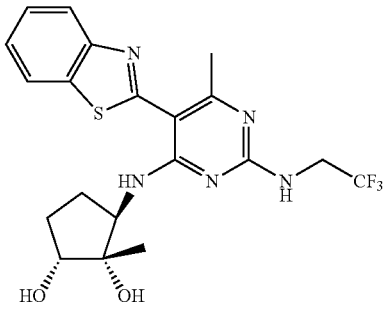
Step 6:

The (1S,2R,5R)-5-(5-(benzo[d]thiazol-2-yl)-6-methyl-2-(methylsulfinyl)pyrimidin-4-ylamino)-1-methylcyclopentane-1,2-diol (1701f) (0.248 mmol, 104 mg) was dissolved in cyclopropylmethanamine (2 mL, by 83-85° C.) and heated in a sealed tube (oil bath 100° C.) for 17 h. LCMS showed complete conversion into product. The volatiles were removed in rotavap and the residue was dissolved in DCM (5 mL) and purified on a Redisep (24 g) silica gel column (gradient: 0 to 60% ethyl acetate in hexanes) to give the product 1701 (90 mg, 88%) as a white solid.

Example 1702

Procedure Z68

1702

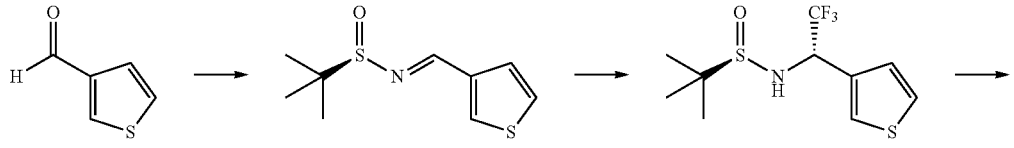


Step 1:

Synthesized from 1701f (104 mg) and 2,2,2-trifluoroethanamine following the procedure Z67, step 6 to give 1702. Purified in semiprep-HPLC and isolated as HCl salt (60 mg, 51%)

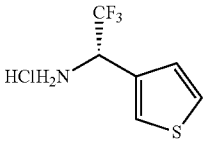
Example 1703

Procedure Z69

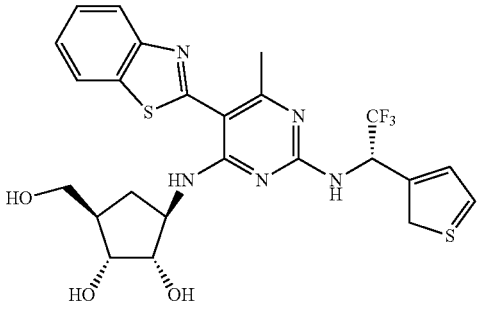


1703a 1703b 1703c

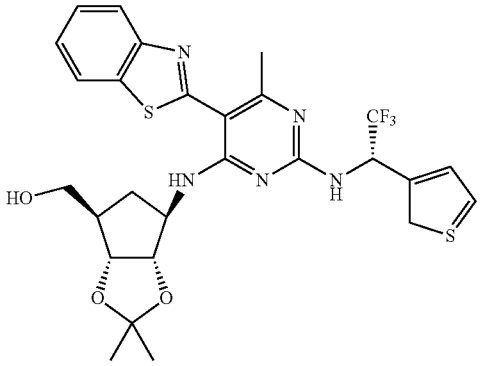
-continued



1703d



1703



1703e

Step 1:

Intermediate 1703b (3.15 g, 81%) was synthesized from thiopehe-3-carboxaldehyde (1703a, 2.03 g, Aldrich) following the procedure described in *J. Org. Chem.* 1999, 64, 1278-1284.

Step 2:

Intermediate 1703c (1.1 g, 42%) was synthesized from 1703b (2.0 g) following the procedure described in *Angew. Chem. Int. Ed.* 2001, 40, 589-590.

Step 3:

A solution of (R)-2-methyl-N—((S)-2,2,2-trifluoro-1-(thiophen-3-yl)ethyl)propane-2-sulfinamide 1703c (1.1 g, 3.85 mmol) in 40 mL of methanol was treated with 4 M HCl in dioxane (8 mL). The mixture was stirred for 10 min and TLC (30% ethyl acetate in hexanes) showed complete consumption of the starting material. All the volatiles were removed in rotavap and the residue was treated with dichloromethane to make a homogeneous solution. Hexanes (50 mL) was added and the mixture was concentrated in rotavap to half its volume. More hexanes (50 mL) was added to the resulting slurry and the mixture was concentrated to half its volume again. The solids were recovered by filtration (whatman #1) to give the product 1703d (780 mg, 95%) as a white solid.

Step 4:

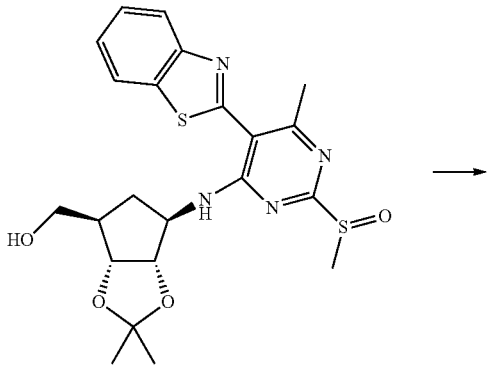
1703e was obtained from 1703d in 62% yield (110 mg) as described in Procedure U, step 5 using dioxane as solvent and purification was done by chromatography on silica gel.

Step 5:

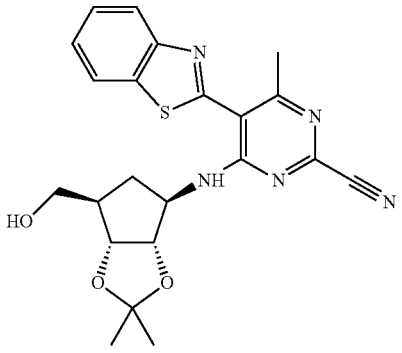
1703 was obtained from 1703e (90 mg) as the hydrochloric salt (80 mg, 97%) as described in Procedure U, step 6.

Example 1901

Procedure Z70



252b

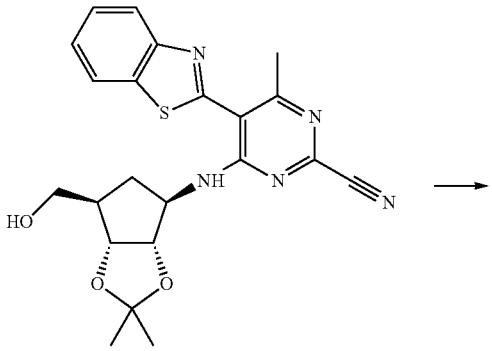


1901

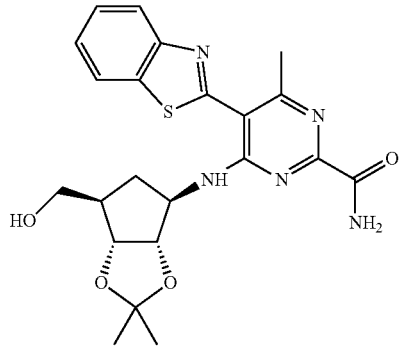
A solution of sulfoxide 252b (333 mg, 0.678 mmol) in anhydrous Dichloromethane (5 ml) was treated with tetrabutylammonium cyanide (182 mg, 0.678 mmol) at room temperature for 4 hours. The solvent was evaporated and the mixture was purified on a silica gel column with 0-80% EtOAc/Hexanes to give a light yellow solid 1901 (243 mg).

Example 1902

Procedure Z71



1901

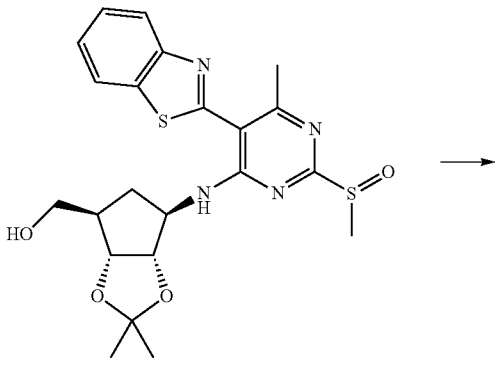


1902

A solution of nitrile compound 1901 (100 mg, 0.2285 mmol) in Tetrahydrofuran (2 ml) and Methanol (2 ml) was cooled to 0° C. and treated with potassium carbonate (47.3 mg, 0.3427 mmol) and hydrogen peroxide (0.7 ml) and allowed to warm to room temperature. The reaction was stirred for 1 hour. TLC #1 with 70% EtOAc/Hexanes shows all starting material was consumed. The THF was removed by evaporation and DCM was added. The DCM was washed with 50% sodium thiosulfate/sodium bicarbonate solution. The DCM layer was dried and evaporated to give a pale yellow solid 1902, (94 mg).

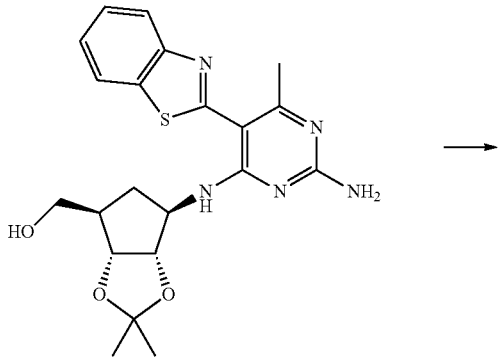
Example 1905

Procedure Z72

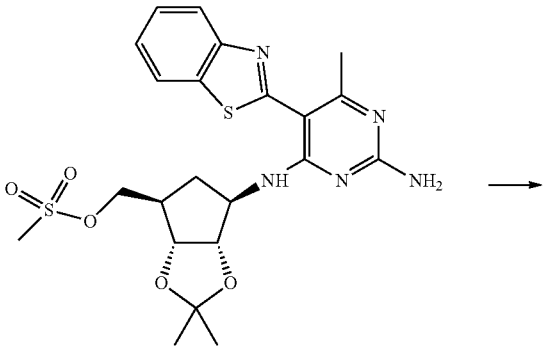


252b

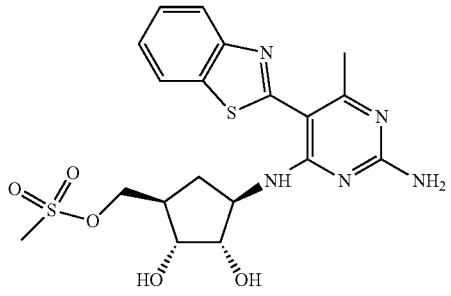
-continued



1905a



1905b



1905

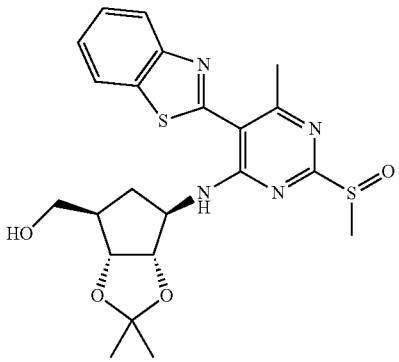
Step A: A solution of sulfoxide 252b (~500 mg, 1.053 mmol) in tetrahydrofuran (10 ml) was treated with ammonium hydroxide (2.5 ml) in a sealed flask and heated to 50° C. for 5 hours. The solvent was removed and the crude was purified on a silica gel column with 0-70% Acetone/Hexanes to give a white solid 1905a (225 mg).

Step B: A solution of amine 1905a (50 mg, 0.1169 mmol) in chloroform (1.5 ml) was treated with triethyl amine (24.4 ul, 0.1753 mmol) and mesyl chloride (9.05 ul, 0.1169 mmol) and stirred at rt for 16 hours. A second equivalent of reagents were added and the reaction was stirred for an additional 2 hours. The solvent was removed and the product was purified on 1000 um silica gel prep plates with 2 elutions of 50% Acetone/Hexanes to give 1905b (24 mg).

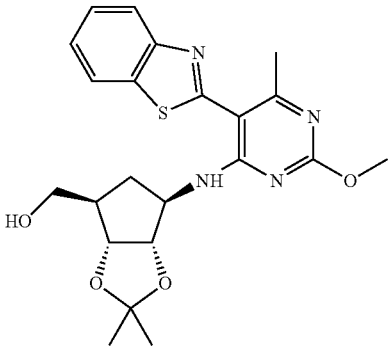
Step C: Compound 1905b was converted to 1905HCl salt using Procedure F, step 3.

Example 1907

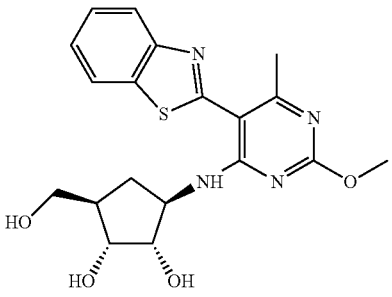
Procedure Z73



252b



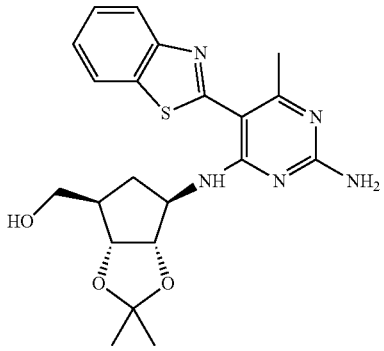
1907a



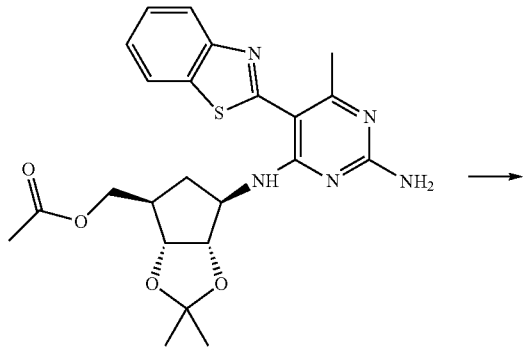
1907

Example 1915

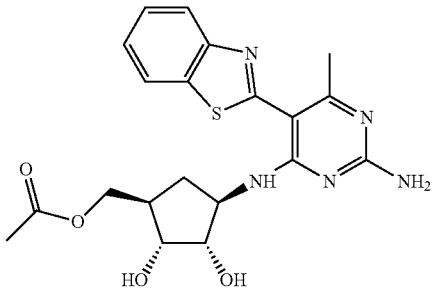
Procedure Z74



1905a



1915a



1915

Step A: A solution of sulfoxide 252b (100 mg, 0.2107 mmol) in Methanol (2 ml) was treated with potassium carbonate (1.0 mmol) at room temperature for 72 hours. The methanol was removed by evaporation, ethyl acetate was added, washed with water and dried over sodium sulfate. The mixture was filtered and solvent removed to give crude product. The residue was purified on a silica gel column with 0-100% Ethyl acetate/Hexanes to give a white solid 1907a (40 mg).

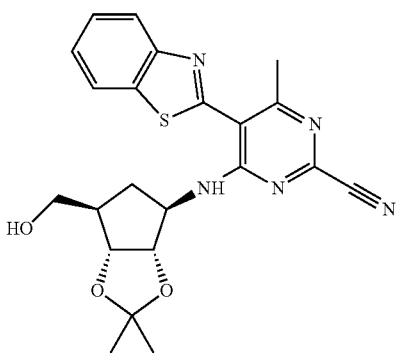
Step B: Compound 1907a was converted to 1907HCl salt using Procedure F, step 3.

Step A: A solution of amine 1905a (50 mg, 0.1169 mmol) in chloroform (1.5 ml) was treated with triethyl amine (24.4 ul, 0.1753 mmol) and acetyl chloride (8.31 ul, 0.1169 mmol) and stirred at rt for 3 hours. A second equivalent of reagents were added and the reaction was stirred for an additional 3 hours. The solvent was removed and the product was purified on a silica gel column with 0-100% EtOAc/Hexanes to give a white solid 1915a (31 mg).

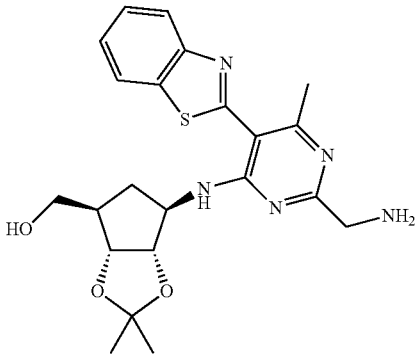
Step B: Compound 1915a was converted to 1915HCl salt using Procedure F, step 3, then purified on C18 reverse phase column eluting with 10-70% THF/Water/TFA to give 1915 TFA salt.

Example 1916

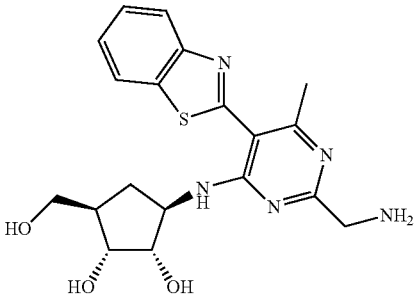
Procedure Z75



1901



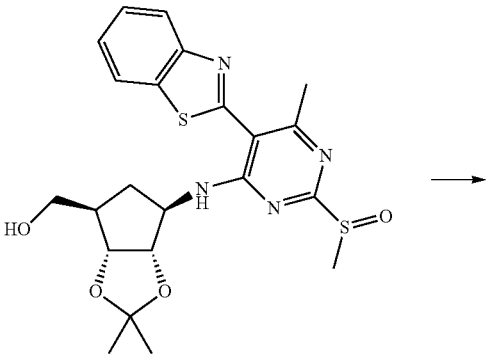
1916a



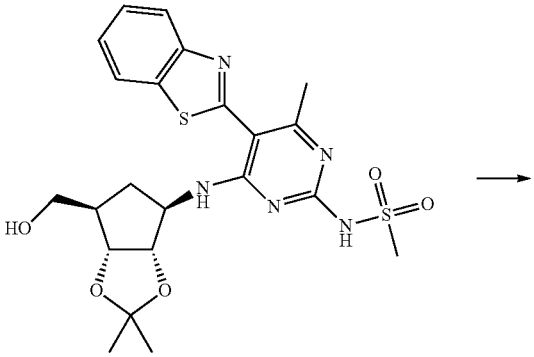
1916

Example 1917

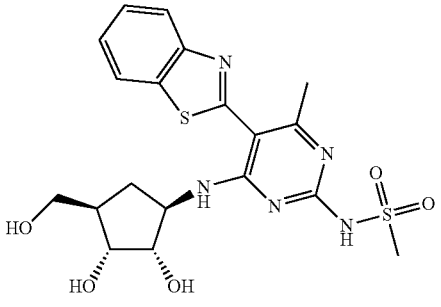
Procedure Z76



252b



1917a



1917

Step A: A solution of Nitrile compound 1901 (125 mg, 0.2857 mmol) was dissolved in Tetrahydrofuran (4.5 ml) and Methanol (0.5 ml), cooled to 0° C. in ice bath and treated with cobalt chloride (74.2 mg, 0.5714 mmol) then portion by portion with the sodium borohydride (108 mg, 2.857 mmol) over 30 minutes and stirred at 0° C. for 1 hour. The solvent was removed by evaporation. EtOAc was added to residue and washed with sat. sodium bicarbonate solution and brine. The EtOAc layer was dried and evaporated to give crude 1916a (71 mg).

Step B: Compound 1916a was converted to crude 1916 using Procedure F, step 3, then purified on C18 reverse phase column eluting with 10-70% THF/Water/TFA to give 1916 TFA salt (21 mg).

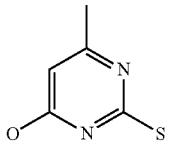
Step A: A solution of methanesulfonamide (114.2 mg, 1.201 mmol) in anhydrous THF (1.5 ml) was cooled to 0° C. and treated with NaH (48 mg, 60% in oil) in one portion. The reaction was allowed to warm to room temperature then stirred for 30 minutes. The reaction was again cooled to 0° C., the sulfoxide 252b (57 mg, 0.1201 mmol) was added and stirred for 0.25 hours again allowing to warm to room temperature then stirred 16 hours. The reaction was made acidic with 1N HCl. EtOAc was added then washed with sat. sodium bicarbonate, 2× with water, brine and filtered through sodium sulfate. The solvent was removed and the residue was purified on a silica gel column with 0-60% THF/Hexanes to give a white solid 1917a (17 mg).

Step B: Compound 1917a was converted to crude 1917HCl salt using Procedure F, step 3, then purified on C18

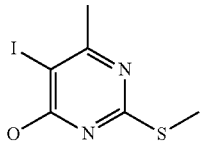
reverse phase column eluting with 10-90% Acetonitrile/Water/TFA to give 1917 TFA salt (12 mg).

Example 31

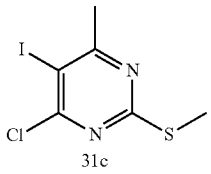
Procedure A-3



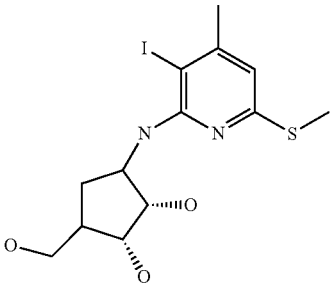
31a



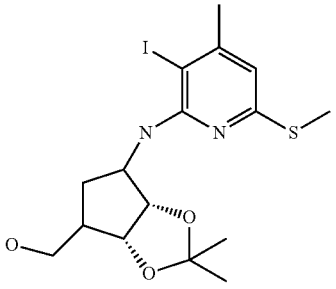
31b



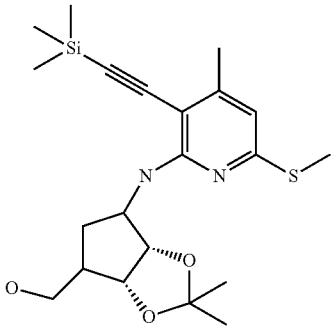
31c



31d



31e



31f

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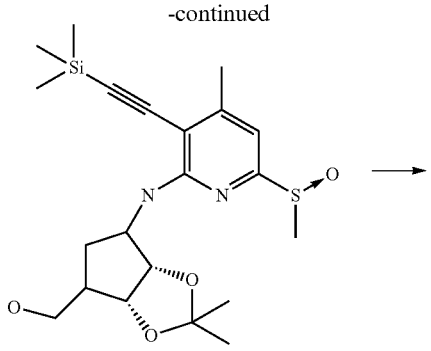
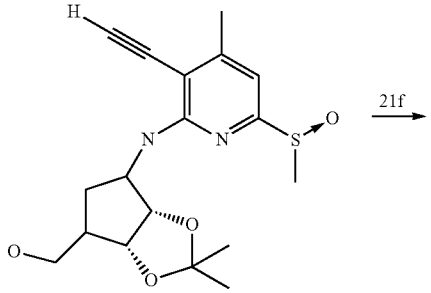
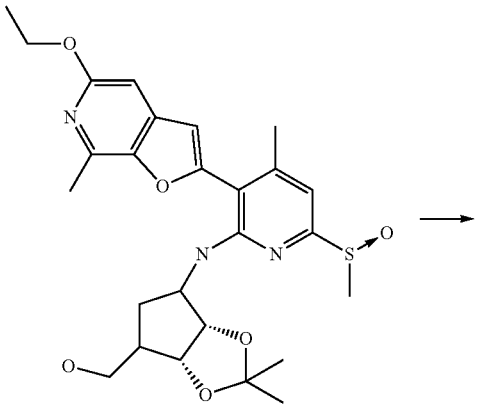


31g

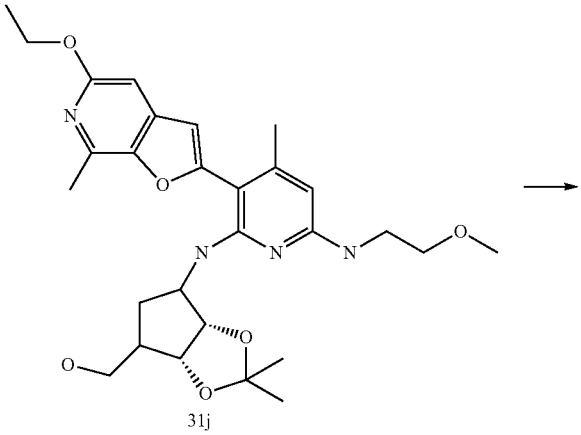


21f

31h

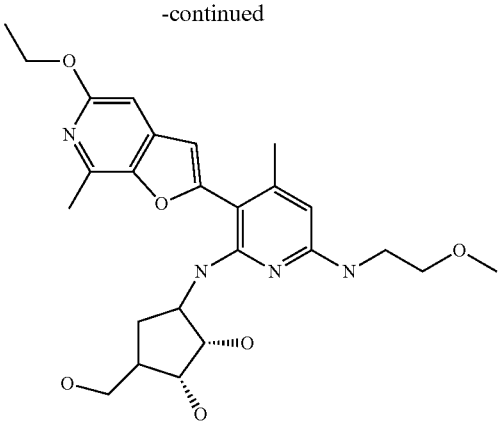


31i



31j

-continued



31

2-Methylthio-4-methyl-6-hydroxypyrimidine 31a was prepared according to the method in (*J. Med. Chem.*, 2007, 50, 1146-57.

2-Methylthio-4-methyl-5-iodo-6-hydroxypyrimidine 31b was prepared from 31a according to the method in *Chem. Pharm. Bull.*, 1986, 34, 2719.

2-Methylthio-4-methyl-5-iodo-6-chloropyrimidine 31c was prepared from 31b according to the method in *Chem. Pharm. Bull.*, 1986, 34, 2719.

Step 1: To a stirred mixture of the chloropyrimidine (2-methylthio-4-Me-5-iodo-6-chloropyrimidine, 51.6 g, 0.172 mol) and the cyclopentylamine carbasugar (34.6 g, 0.189 mol) in EtOH was added diisopropylethylamine (100 mL, 0.566 mol). The resulting mixture was refluxed overnight, becoming a solution after ~1 h of heating. After TLC showed that a small amount of the starting chloropyrimidine present, another 0.1 eq of the cyclopentylamine carbasugar (3.46 g) and more diisopropylethylamine (10 mL) were added and while heating a mixture was formed. After refluxing overnight, the reaction was allowed to cool to room temperature and to set for ~2 h. The resulting precipitated solid was filtered and collected, washed with EtOH, and dried under high vacuum to give a 79% yield of the desired adduct as an off-white solid. The filtrate was chromatographed on silica gel eluting with a chloroform/methanol (grad. 0 to 10% MeOH) to give more of the desired adduct 31d as a slightly impure solid product (total yield was ess. quantitative).

Step 2: Carbasugar adduct 31d (ess. 14.1 g, 35 mmol) was suspended in acetone (200 mL), and dimethoxypropane (8.6 mL, 7.3 g, 70 mmol) was added, followed by methanesulfonic acid (2.3 mL, 3.4 g, 35 mmol). The reaction was allowed to stir overnight becoming a solution over time. After concentrating the reaction mixture, the residue was taken up in methylene chloride and washed with saturated aqueous $NaHCO_3$, dried over sodium sulfate, and concentrated. After silica gel chromatographing eluting with chloroform/methanol (grd. 0 to 5%), the desired product 31e (11.99 g, 75.7% yield) was isolated as a white foam.

Step 3: Argon was bubbled through a stirred mixture of carbasugar protected 31e (11.99 g, 26.5 mmol) in anhydrous dioxane (175 mL), and then, Et_3N (14.8 mL, 106 mmol) was added, followed by CuI (1.01 mg, 5.3 mmol) and $(Ph_3P)_2PdCl_2$ (1.86 g, 2.65 mmol). The reaction vessel was sealed with a rubber septum equipped with an outlet needle, and the deoxygenation of the vessel with bubbling argon was continued for another ~10 min, TMS acetylene (11.2 mL, 79.5 mmol) was added, and the reaction sealed and protected from light. The reaction was then heated on a 50° oil bath for ~20 h. The reaction mixture was concentrated under vacuum and then partitioned with methylene chloride and water. The organic extract was washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel eluting with chloroform/methanol (grad. 0 to 2% MeOH) to giving 31f (10.47 g, 93.6%) as a dark, highly colored foam or viscous glass.

Step 4: To a stirred methylene chloride (40 mL) solution of 31f (1.0 g, 2.4 mmol), cooled in an ice/water bath, was added mCPBA (655 mg, 2.8 mmol) in one aliquot. After ~1 h saturated aq. $Na_2S_2O_3$ was then added, and the mixture was diluted with methylene chloride and water. The organic extract was washed with water, saturated brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel eluting with chloroform/methanol (grd. 0 to 5% MeOH). Sulfoxide 31g (747 mg, 71.1%) was isolated as a mixture of diastereomers (by NMR). A small amount (146 mg) of the sulfone corresponding to 31g was also isolated.

Step 5: To a solution of sulfoxide 31g (747 mg, 1.71 mmol) in CH_3CN under argon with stirring was added $Et_4NF.2H_2O$ (106 mg, 0.57 mmol). The reaction was allowed to stir overnight then chromatographed on silica gel eluting with chloroform/methanol (grad. 0 to 4% MeOH). Product 31h was isolated as a slightly colored foam (515 mg, 82.4% yield).

Step 6:

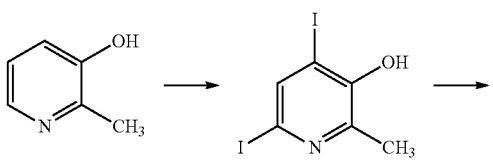
While bubbling argon through a solution of 31h (183 mg, 0.5 mmol) and 21f (167 mg, 0.6 mmol) in DMF (3 mL), Et_3N (0.35 mL, 2.5 mmol) was added, followed by CuI (19 mg, 0.1 mmol). After 10 min stirring, $(Ph_3P)_4Pd$ (58 mg, 0.05 mmol) was added, and after another ~2 min of argon bubbling, the reaction tube was capped and microwaved at 300 W at 90° C. for 10 min. The reaction mixture was then concentrated, taken up in MeOH, and filtered. The filtrate was chromatographed on silica gel eluting with chloroform/methanol (grad. 0 to 5% MeOH). The desired product 31i was isolated as a yellow foam (232 mg, 89.8% yield).

Step 7: To a solution of sulfoxide 31i (100 mg, 0.194 mmol) in acetonitrile (5 mL) was added methoxyethylamine (0.17 ml, 1.94 mmol). The resulting solution was refluxed overnight. After cooling to room temperature, a solid formed which was isolated by filtration, collected, washed with acetonitrile, and then dried under vacuum. The obtained grayish solid was the desired product 31j (42 mg, 41.2% yield).

Step 8: To a solution of isopropylidene 31j (40 mg, 0.076 mmol) in MeOH (3 mL) was added aqueous 1N HCl and stirred overnight. The reaction was then filtered and concentrated to give the desired product 31 as a yellow solid as its HCl salt (48 mg, product contains 0.5 eq of MeOH).

Example 48

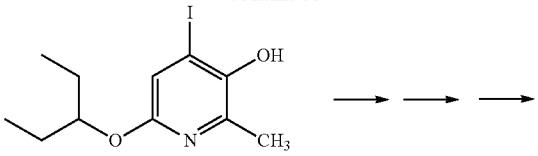
Procedure A-4



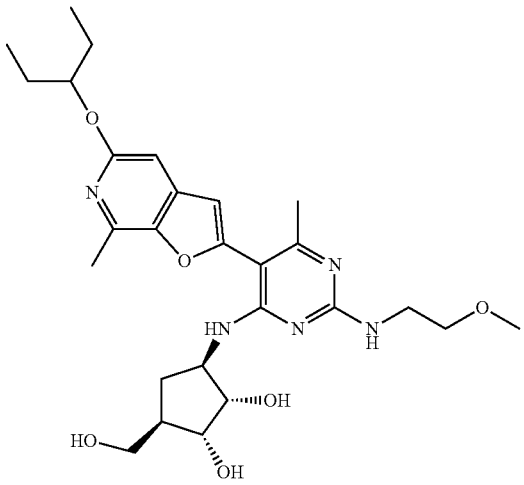
21A

48B

-continued



48C



48

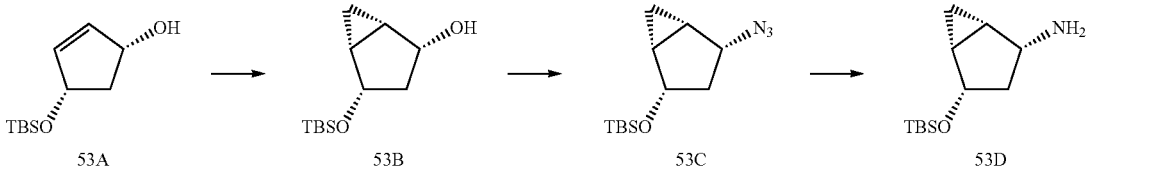
After a solution of aqueous K_2CO_3 (106.4 g in 350 mL) was cooled to room temp, compound 21A (24.0 g, 0.22 mol) was added, and the resulting solution was placed in an ice bath and stirred for ~25 min. Then, solid I_2 (112.0 g (0.44 mol) was added in one portion, and the resulting suspension was left to warm to room temp overnight with stirring. The suspension was then treated with a concentrated sodium thiosulfate solution (~60 mL), and then conc. HCl (~115 ml) was added dropwise with via an addition funnel at a rate that avoided clumping. (The addition of a little EtOAc helped to separate any clumps that formed. The pH of the resulting suspension is about 2-3 by pH paper.) The resulting mixture was then extracted with EtOAc (3×150 mL) and the combined organic layers washed with brine (1×400 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. Flash chromatography eluting with a stepwise gradient of 0 to 25% EtOAc in hexanes afforded compound 48B (TLC in 1:4 EtOAc/hexane, R_f 48B=~0.4).

A mixture of 3-pentanol (1.5 mL, 0.013 mol) and 4 Å molecular sieves (~0.7 g, crushed and activated) in THF (50 mL) was stirred for ~10 min at room temp under argon). NaH was then added in portions over ~5 min, and the mixture was allowed to stir until H2 evolution ceased (~5 min). To this mixture was added 48B (2.5 g, 6.9 mmol) followed by CuBr (0.2 g, 0.0013 mol), and the mixture was placed in an oil bath maintained at 85-90° C. After 2 h, TLC showed that the starting material was essentially consumed, and the mixture was filtered through Celite and washed with a minimal amount of CH_2Cl_2. The solvent was then removed in vacuo, and the residue was partitioned between EtOAc and ~0.5 M HCl (15 mL each). The organic layer was separated and washed with sodium thiosulfate (1×15 mL), brine (1×15 mL) and concentrated to dryness. The residue was then preadsorbed onto silica gel (coarse, ~8.0 g) and purified by flash chromatography, eluting with a stepwise gradient of 0 to 25% EtOAc in hexanes, affording compound 48C (1.5 g).

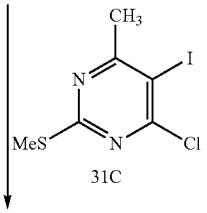
48C was then used in place of 21f in Procedure A-3, and following the same essential procedure, target 48 was obtained.

Example 53

Procedure A-5

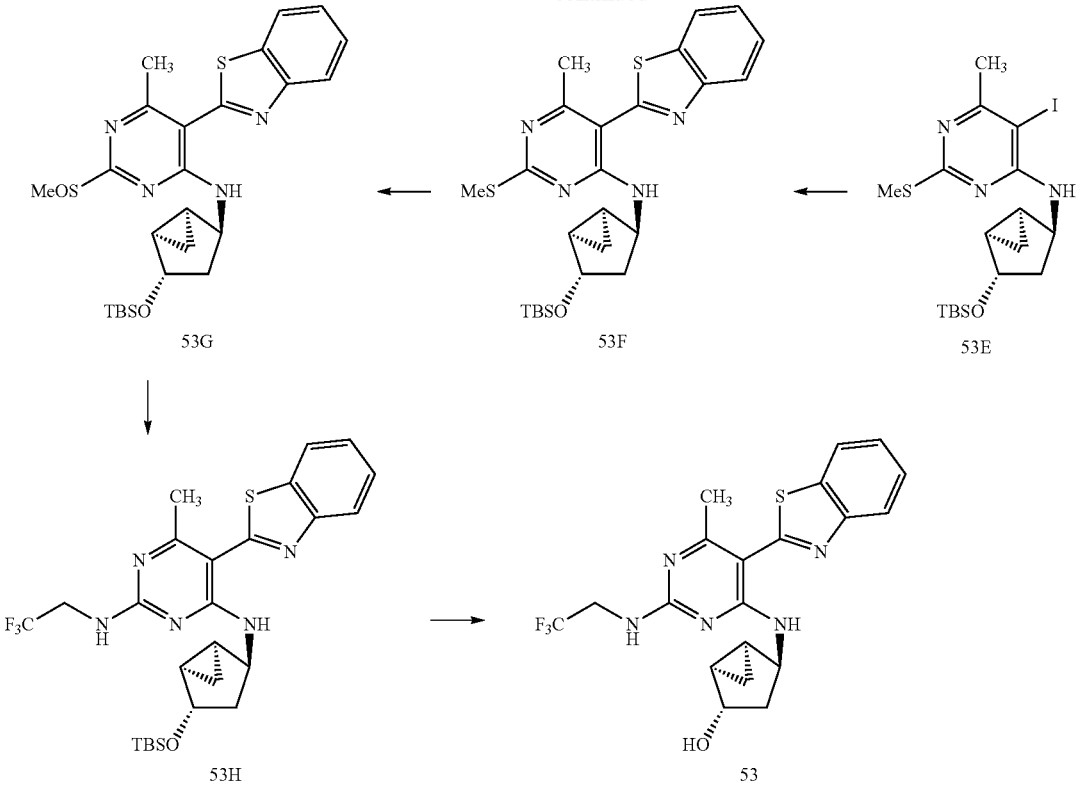


53A 53B 53C 53D



31C

-continued



To a solution of 53A (1.0 g, 4.66 mmol) in methylene chloride (30 ml) was added diethyl zinc solution (5.4 ml, 1M hexanes, 5.36 mmol) at a rate to keep the temperature at <2° C. After the addition was complete, a solution of diiodomethane (0.43 ml, 5.36 mmol) in methylene chloride (2.3 ml) was added in one portion. After 15 min, another portion of diethyl zinc solution (5.4 ml, 1M hexanes, 5.36 mmol) was added at a rate to keep the temperature at <2° C., and then after 15 min, another solution of diiodomethane (0.43 ml, 5.36 mmol) in methylene chloride (2.3 ml) was added in one portion. After 15 min, the resulting mixture was allowed to warm to room temperature, and then, after 4 h, the reaction was quenched with saturated ammonium chloride and diluted with methylene chloride and saturated ammonium chloride. After separating the layers, the aqueous layer was further extracted with methylene chloride (3×), and the combined organic extracts were dried with sodium sulfate and then concentrated. Compound 53B (1.02 g) was obtained as a slightly yellow crystalline solid.

To a solution of 53B (988 mg, 4.32 mmol) and triphenyl phosphine (2.84 g, 10.8 mmol) in tetrahydrofuran (25 ml), diisopropyl azodicarboxylate (1.70 ml, 8.65 mmol) was added at a rate to keep the temperature between −20° C. and -18° C. After the addition was complete, diphenylphosphoryl azide (0.93 ml, 4.32 mmol) was added dropwise. The resulting mixture was then allowed to warm to room temperature and left overnight. The reaction was partitioned between ethyl ether and saturated brine, the aqueous layer was further extracted with ethyl ether (2×), and the combined organic extracts were dried sodium sulfate and concentrated. The recovered 5.3 g of crude product was chromatographed on silica, eluting with EtOAc/hexanes (gradient 0/100→10/90). Compound 53C (637 mg) was obtained as a clear oil.

To a stirred solution of 53C (278 mg, 1.1 mmol) and triphenyl phosphine (360 mg, 1.37 mmol) in tetrahydrofuran (5 ml) was added water (0.5 ml). After 3 days, the resulting mixture was concentrated and coevaporated with ethanol (3×). The crude reaction mixture containing 53D was combined with chloropyrimidine 31C (413 mg, 1.38 mmol) in ethanol, and diisopropylethyl amine (0.72 ml, 3.75 mmol) was added. The resulting mixture was then refluxed for 2 days and then concentrated and chromatographed on silica, eluting with a gradient of methylene chloride/methanol (100/0, then gradient 100/0→98/2). Compound 53E (344 mg) was obtained as a clear oil.

To an argon-flushed flask containing 53E (344 mg, 0.70 mmol) was added copper(I) iodide (33 mg, 0.17 mmol) followed by tetrakistriphenylphosphine palladium (121 mg, 0.10 mmol), cesium carbonate (1.14 g, 3.5 mmol), benzothiazole (0.15 ml, 1.4 mmol) and DMF (10 ml), sequentially. After degassing with Ar for 10 min, the flask was by sealed with a rubber septum and was heated in a preheated oil bath at 100° C. for 4 h. After diluting with ethyl acetate, the mixture was filtered through a celite pad, washing with ethyl acetate. The filtrate was diluted with ethyl acetate and combined organic extract washed with water (2×) and saturated brine, dried with sodium sulfate and concentrated. After chromatography on silica eluting with chloroform/methanol (100/0, then gradient 100/0→98/2), compound 53F (178 mg) was recovered as a slightly yellow solid.

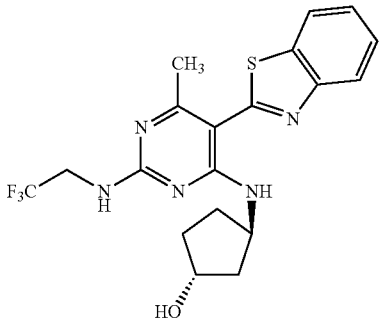
To an ice water bath-cooled solution of sulfide 53F (178 mg, 0.36 mmol) in methylene chloride (10 ml) was added MCPBA (82 mg, ~75% purity, 0.36 mmol). After 1 h, more MCPBA (8 mg) was added. The reaction was then quenched a few minutes later with saturated sodium thiosulfate. After diluting with methylene chloride, the separated combined

organic extract was washed with a sodium thiosulfate solution and saturated sodium bicarbonate, then dried with sodium sulfate and concentrated. The resulting residue was chromatographed on silica eluting chloroform/methanol (100/0, then gradient 100/0→98/2). Compound 53G (154 mg) was obtained as a slightly yellow solid.

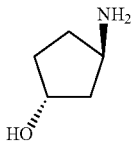
To a microwave reaction vial containing sulfoxide 53G (145 mg, 0.282 mmol) was added trifluoroethylamine (3 ml). The sealed vial was then heated in the microwave at 100° C. for 2 h, then at 125° C. for another 2 h. After concentrating, the resulting residue was chromatographed on silica, eluting with chloroform/methanol (100/0, then gradient 100/0→99/1). Compound 53H (140 mg) was obtained as a slightly yellow solid.

To a solution of 53H (124 mg, 0.23 mmol) in acetonitrile (5 ml) and tetrahydrofuran (5 ml) was added tetraethylammonium fluoride dihydrate (42 mg, 0.23 mmol), and the whole was stirred overnight. Another 42 mg of tetraethylammonium fluoride dihydrate was then added, and stirring was continued for another 24 h. After concentrating, the residue was chromatographed on silica, eluting with chloroform/methanol (gradient 100/0→94/4) giving the free base of 53 (66 mg) as a slightly colored solid. This solid was then suspended in methanol (20 ml) and 1N HCl (3 ml) was added. After concentrating and azeotroping with methanol (3×), compound 53 (66 mg) was obtained as a white solid.

Example 54



54

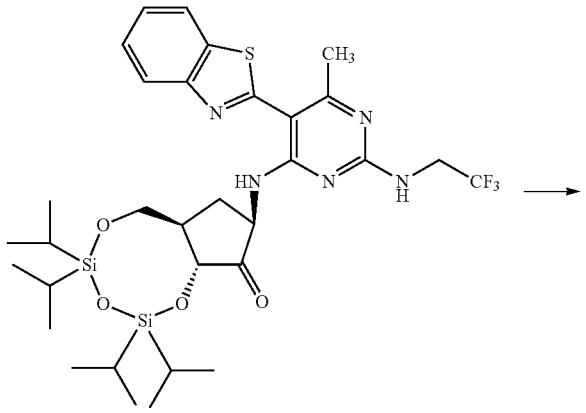


54A

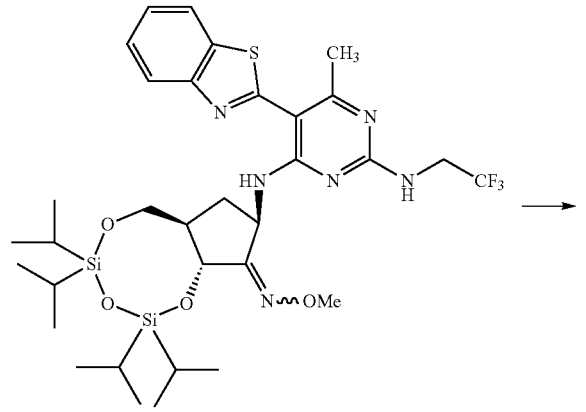
Compound 54 was also prepared by essentially the above procedure A-5, using the required hydroxycyclopentylamine 54A (WO 077551, 2008) instead of cyclopentylamine 53D.

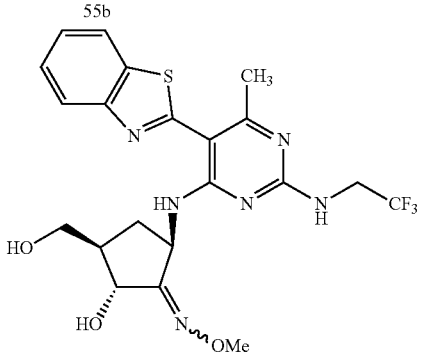
Example 55

Procedure A-6



55a





55

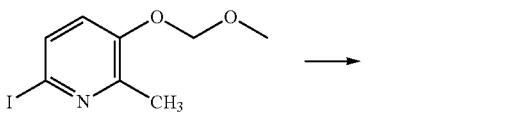
To a solution of 55a (prepared in a similar manner to 1383d, procedure Z43, 94 mg, 0.13 mmol) in pyridine (5 ml), diethyl O-methylhydroxylamine hydrochloride (13 mg, 0.16 mmol) was added. After stirring overnight and concentrating, the residue was partitioned with chloroform and saturated aqueous sodium bicarbonate. The organic extract was dried over sodium sulfate and then concentrated. Chromatography of the residue on silica gel, eluting with a gradient of EtOAc/hexanes (0/100→20/80) gave 55b (86 mg) as a solid.

To a solution of 55b (85 mg, 0.115 mmol) in acetonitrile (8 ml) was added tetraethyl-ammonium fluoride dihydrate

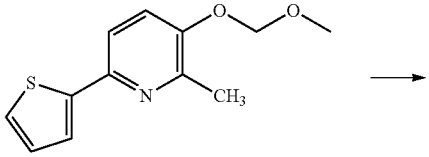
(21 mg, 0.115 mmol), and the mixture was stirred overnight. After concentrating, the residue was chromatographed on silica gel, eluting with a gradient of chloroform/methanol (100/0→95/5), giving 55 (49 mg) as a slightly colored solid that was a mixture of oxime isomers.

Example 43

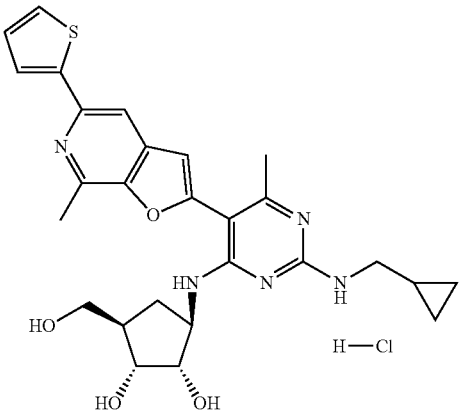
Procedure A-7



21c



43a

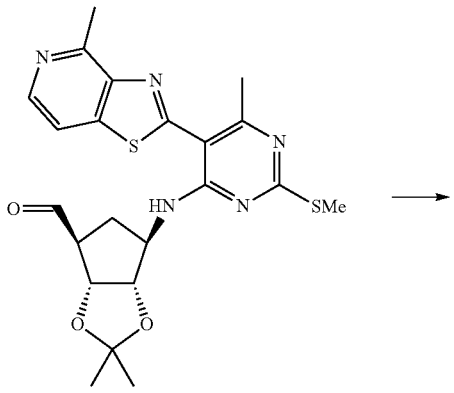


43

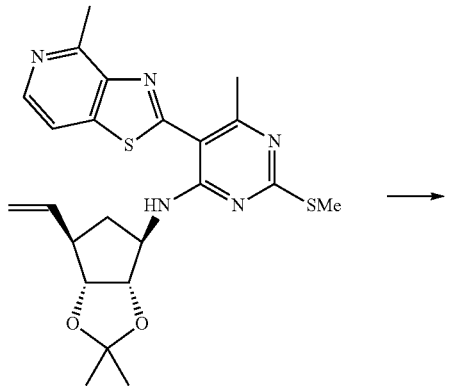
To a solution of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)dichloride (31 mg, 0.045 mmol) and lithium bromide (780 g, 8.99 mmol) in tetrahydrofuran (10 ml) and 1,3-dimethyl-2-imidazolidinone (10 ml), was added a solution of thienylzinc bromide (9.0 ml, 0.5M THF, 4.5 mmol). A solution of 21c (783 mg, 2.80 mmol) in 1,3-dimethyl-2-imidazolidinone (5 ml) was then cannulated into the reaction, followed by tetrahydrofuran (10 ml). After 3 h, the mixture was diluted with ethyl ether (50 ml) and washed with 1M ethylenediaminetetraacetic acid trisodium salt solution, followed by washing with water and brine, then dried with sodium sulfate and concentrated. Chromatography on silica gel, eluting with a gradient of EtOAc/hexanes (0/100→15/85), gave an oil comprised of a 3:1 ratio of 21c:43a, (637 mg). Then, to a solution of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)dichloride (31 mg, 0.045 mmol) and lithium bromide (780 mg, 8.99 mmol) in tetrahydrofuran (10 ml) and 1,3-dimethyl-2-imidazolidinone (10 ml) was cannulated a solution of the above mixture of 21c:43a (664 mg) in 1,3-dimethyl-2-imidazolidinone (5 ml), followed by tetrahydrofuran (10 ml). A solution of thienylzinc bromide (9.0 ml, 0.5M THF, 4.5 mmol) was added, and this solution was refluxed overnight. After diluting with ethyl ether (50 ml), the mixture was washed with 1M ethylenediaminetetraacetic acid trisodium salt solution, water, and brine, and then dried over sodium sulfate and concentrated. Chromatography on silica gel eluting gradient of EtOAc/hexanes (0/100→20/80) yielded 43a (478 mg) as a yellow oil.

Subsequent conversion of 43a to compound 43 followed appropriate reaction sequences from procedures A-2 and A-3.

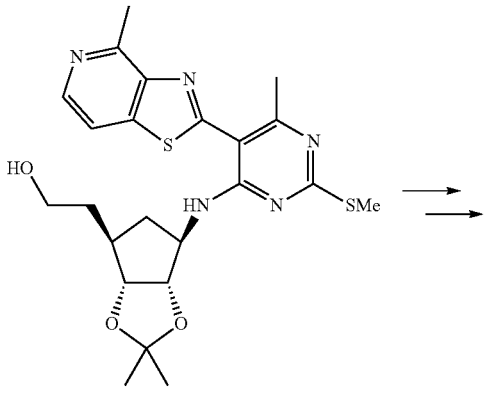
Preparation of 3541:



3541A

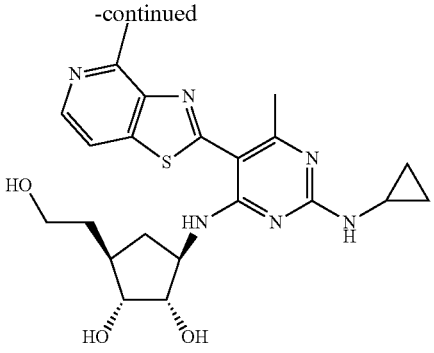


3541B



3541C

-continued



3541

Compound 3541A was synthesized using chemistry in Procedure Z1.

Step 1:

Methyltriphenylphosphonium bromide (1.8 g, 5.27 mmol) was suspended in THF (20 mL) and treated with 0.5 M potassium hexamethyldisilazide solution (10.5 mL). The yellow suspension was cooled in an ice bath and compound 3541A (1.0 g, 2.11 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for two hours and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (1:1 hexanes/ethyl acetate) to provide 3541B (800 mg). Yield: 81% [M+H]=470.25

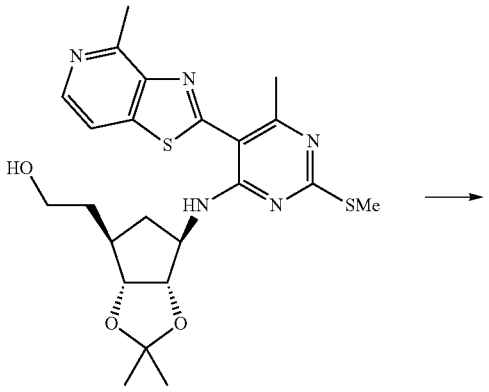
Step 2:

Compound 3541B (800 mg, 1.7 mmol) was dissolved in THF (20 mL) and cooled in an ice bath before a 0.5 M solution of 9-BBN (20.4 mL, 10.2 mmol) was added dropwise. The reaction was stirred for 2 hours at room temperature and then cooled once again in an ice bath. The reaction was quenched slowly with 50% sodium hydroxide (2 mL) mixed with 30% hydrogen peroxide (0.8 mL). Ethyl acetate and water were added and the organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate→20% MeOH) to provide 3541C (750 mg). Yield: 90% [M+H]=488.3

Step 3:

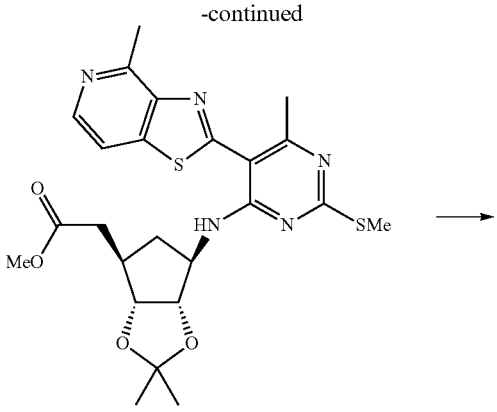
Compound 3541 was synthesized from 3541C using chemistry in Procedure Z1.

Preparation of 3552:

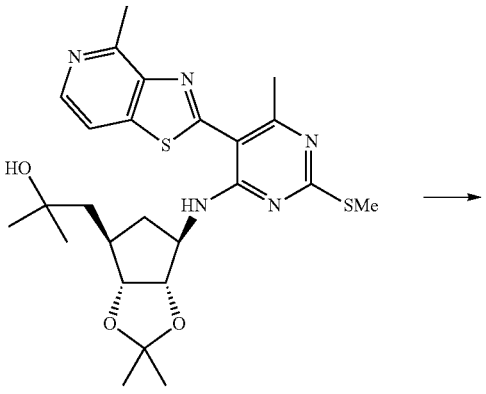


3541C

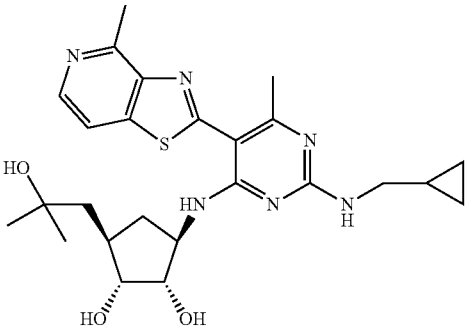
-continued



3552A



3552B



3552

Compound 3541C was synthesized using chemistry in Procedure 3541.

Step 1:

Compound 3541C (217 mg, 0.44 mmol), TEMPO (139 mg, 0.89 mmol), diiodobenzene diacetate (425 mg, 1.32 mmol), CuO (76 mg, 0.88 mmol), and CuI (168 mg, 0.88 mmol) were stirred in methylene chloride (10 mL) overnight. The reaction mixture was filtered over celite and washed with water. The organic layer was dried over sodium sulfate and concentrated to provide the crude acid that was not purified. [M+H]=502.2. The crude acid was dissolved in toluene/methanol (10 mL/10 mL) and 2M TMS diazomethane (5 mL) was added dropwise until bubbling ceased. The reaction was quenched with acetic acid dropwise and then treated with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated. The resi-

due was purified by column chromatography (ethyl acetate→10% methanol) to provide 3552A (120 mg). Yield: 53% [M+H]=516.33

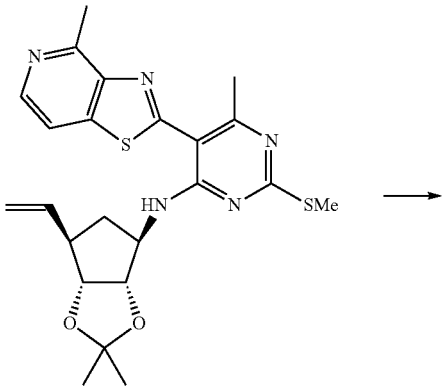
Step 2:

Compound 3552A (120 mg, 0.23 mmol) was dissolved in THF (8 mL) and cooled in an ice bath before the dropwise addition of 3M methylmagnesium bromide (0.8 mL, 2.4 mmol). The reaction was stirred one hour at this temperature and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate→10% methanol) to provide 3552B (65 mg). Yield: 55% [M+H]=516.33

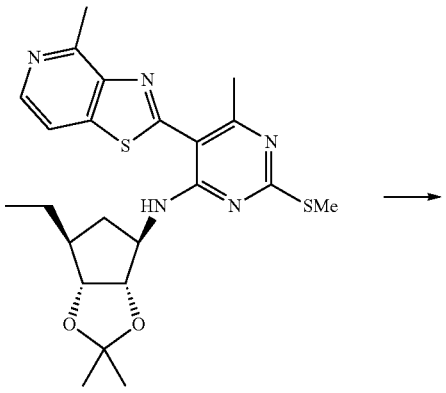
Step 3:

Compound 3552 was synthesized from 3552B using chemistry in Procedure Z1.

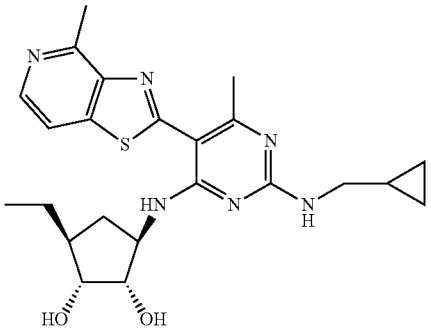
Preparation of 3557:



3541B



3557A



3557

Compound 3541B was synthesized using chemistry in Procedure 3541.

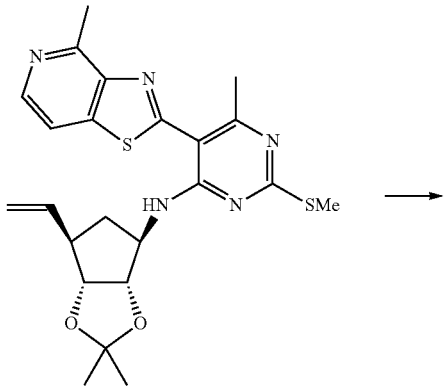
Step 1:

Compound 3541B (212 mg, 0.45 mmol) was dissolved in methanol (10 mL) and treated with 10% Pd—C (0.3 g) under a hydrogen atmosphere (1 atm). After 12 hours the reaction mixture was filtered over celite and concentrated. The residue was purified by column chromatography (ethyl acetate→10% methanol) to provide 3557A (86 mg). Yield: 41% [M+H]=472.31

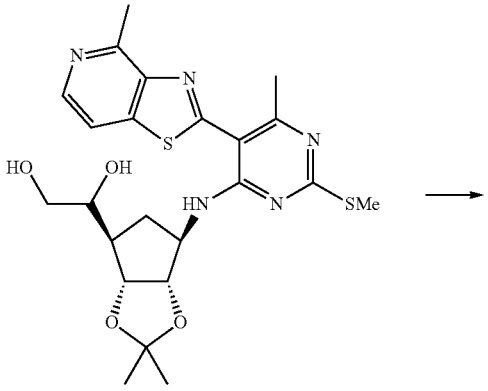
Step 2:

Compound 3557 was synthesized from 3557A using chemistry in Procedure Z1.

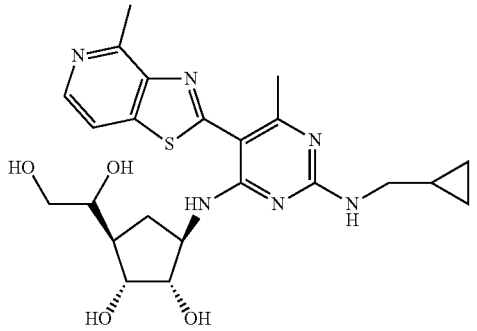
Preparation of 3591:



3541B



3591A



3591

Compound 3541B was synthesized using chemistry in Procedure 3541.

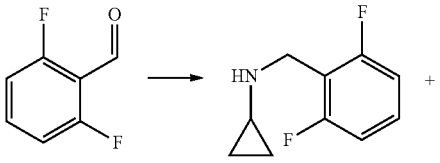
Step 1:

Compound 3541B (2.0 g, 4.25 mmol) was dissolved in THF/water (60 mL/60 mL) and 40% osmium tetroxide in water (2 mL) and NMO (1.25 g, 8.5 mmol) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was extracted with ethyl acetate several times and the combined organic layers were dried over sodium sulfate and concentrated. The residue was triturated with ethyl acetate to provide 3591A (1.5 g). Yield: 70% [M+H]=504.2

Step 2:

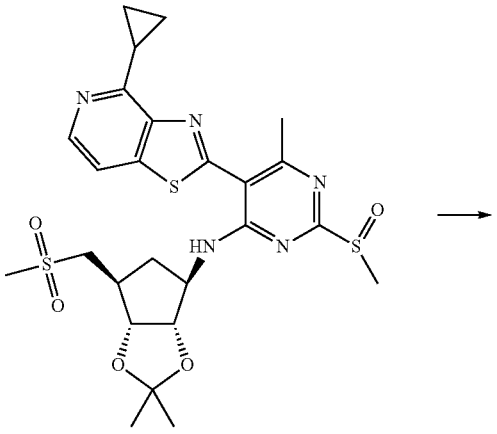
Compound 3591 was synthesized from 3591A using chemistry in Procedure Z1.

Preparation of 3595:

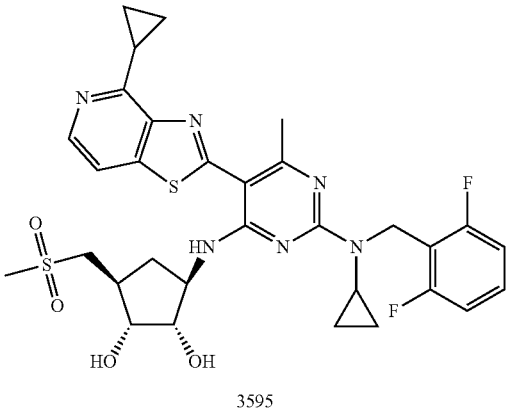


3595A

3595B



3595C



3595

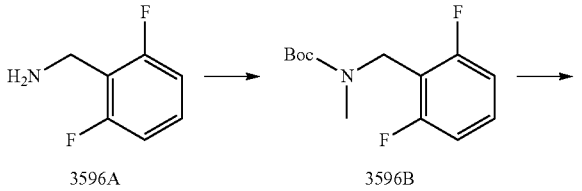
Step 1:

Compound 3595A (500 mg, 3.5 mmol) was dissolved in THF (10 mL) and treated with cyclopropylamine (400 mg, 7 mmol) and stirred for 20 minutes. Sodium borohydride (100 mg) was added slowly and the reaction was stirred for 1 hour at room temperature. The reaction was slowly quenched with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide 3595B that was used without purification (450 mg). Yield: 77%

Step 2:

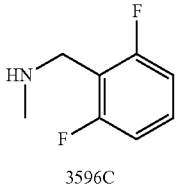
Compound 3595 was synthesized from 3595B and 3595C (synthesis described earlier) using chemistry in Procedure Z1.

Preparation of 3596:

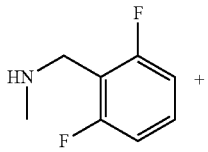


3596A

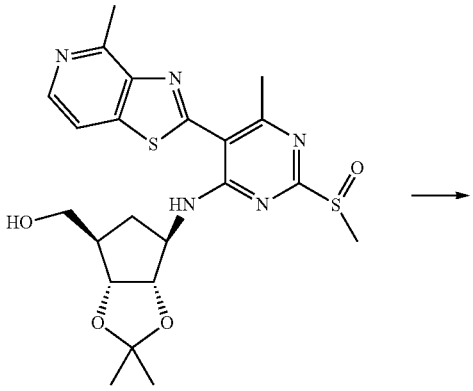
3596B



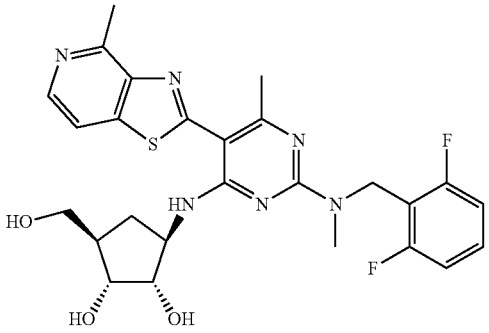
3596C



3596C



3596D



3596

Step 1:

Compound 3596A (500 mg, 3.5 mmol) was dissolved in THF (10 mL) and saturated sodium bicarbonate (10 mL) and then treated with BOC_2O (913 mg, 4.19 mmol). After 1 hour the reaction was quenched with water and then extracted

with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (4:1 hexanes/ethyl acetate) to provide the Boc protected amine (850 mg). The intermediate was dissolved in DMF (10 mL) and treated with 60% NaH (210 mg, 5.22 mmol) after cooling in an ice bath. After 20 minutes at room temperature iodomethane (0.5 mL) was added and the reaction was stirred for 1.5 hours at room temperature. The reaction was quenched with water and then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (10:1 hexanes/ethyl acetate) to provide 3596B (520 mg). Yield: 58%

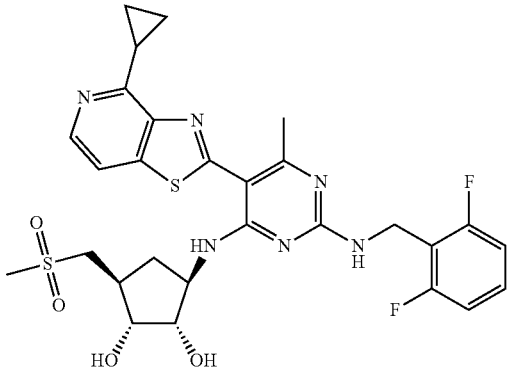
Step 2:

Compound 3596B (520 mg, 2.02 mmol) was dissolved in methanol (5 mL) and treated with 4M HCl dioxane (1 mL). After 1 hour the reaction was quenched slowly with saturated sodium bicarbonate and then extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to provide 3596C (320 mg). Yield 100%

Step 3:

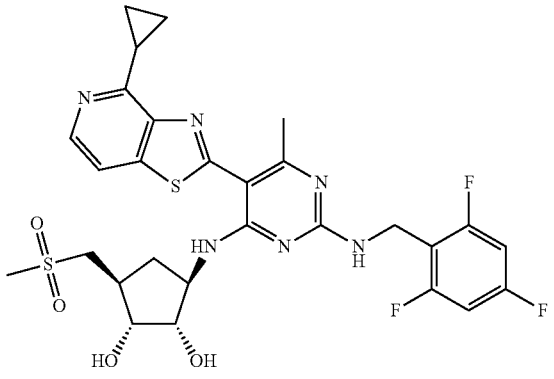
Compound 3596 was synthesized from 3596C and 3596D (synthesis described earlier) using chemistry in Procedure Z1.

Compound 3538:



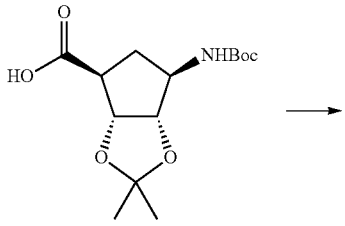
Compound 3538 was synthesized by using earlier described procedures (Z40). 1H NMR (CD3OD-d4) 1.3 (m, 1H), 1.6-1.7 (m, 2H), 1.8-1.85 (m, 2H), 2.50 (s, 3H), 2.5-2.65 (m, 3H), 3.0 (s, 3H), 3.0-3.15 (m, 2H), 3.5-3.6 (m, 1H), 3.8 (m, 1H), 3.85 (m, 1H), 4.8 (d, 2H), 7.1 (m, 2H), 7.4 (m, 1H), 8.5 (m, 2H).

Compound 3563:

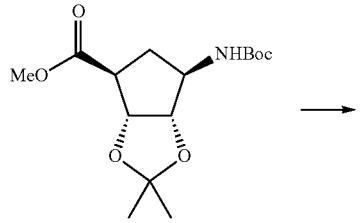


Compound 3563 was synthesized by using earlier described procedures (Z40). 1H NMR (CD3OD-d4) 1.3 (m, 1H), 1.6-1.7 (m, 2H), 1.8-1.82 (m, 2H), 2.50 (s, 3H), 2.5-2.62 (m, 2H), 3.0 (s, 3H), 3.0-3.18 (m, 2H), 3.5 (m, 1H), 3.8 (m, 1H), 3.95 (m, 1H), 4.8 (d, 2H), 7.0 (m, 1H), 7.4 (m, 1H), 8.5 (m, 2H).

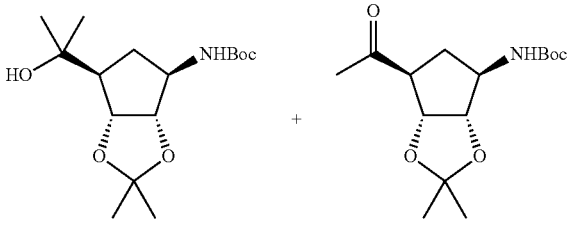
Preparation of 3123:



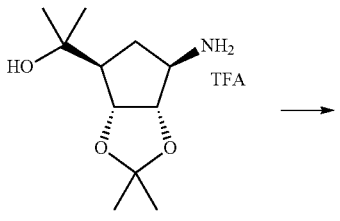
3123a



3123b

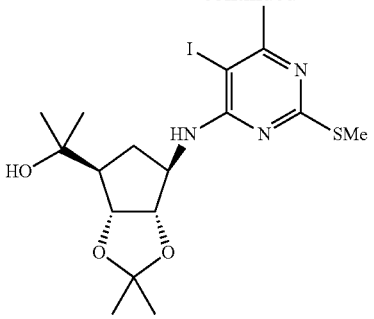


3123c 3123d

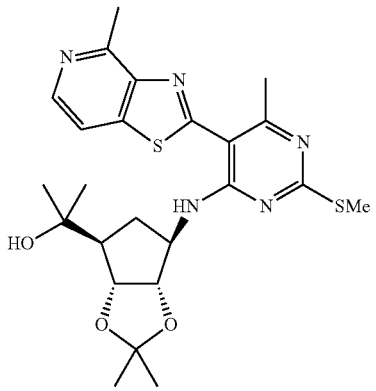


3123e

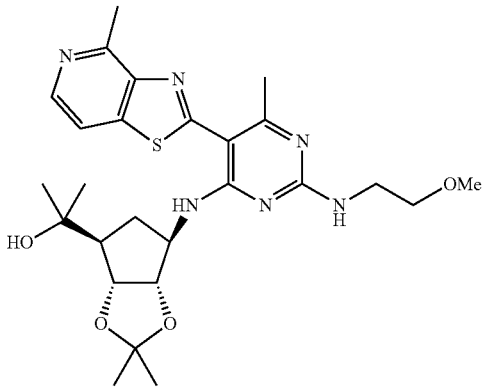
-continued



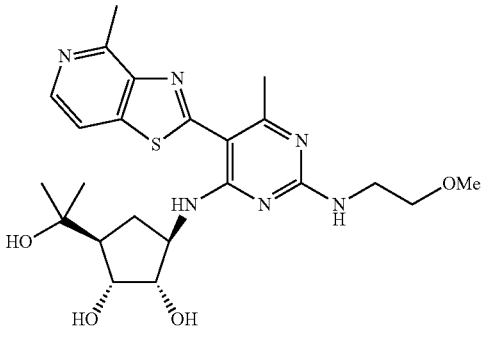
3123f



3123g



3123h



3123

3123b: Acid 3123a (10 g, 33 mmol) was dissolved in MeOH (20 mL) and toluene (100 mL) was then added to the solution. $TMSCH_2N_2$ (2M/hexanes) was then titrated in until the solution retained a yellow tint. AcOH was added dropwise until the solution returned to colorless. The solution was concentrated in vacuo to give 10 g of a white powder that was carried on.

3123c & 3123d: Ester 3123b (9 g, 29 mmol) was dissolved in THF (150 mL) and cooled to −30° C. MeLi (1.6M/Et_2O, 75 mL, 120 mmol) was slowly cannulated in over 15 min and the reaction was allowed to stir at −30° C. for 1 h. Another 0.2 eq of MeLi was then added, and the reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with H_2O (300 mL). The solution was extracted with EtOAc (3×350 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10→60% EtOAc/hexanes) to give 5.7 g of product and 880 mg of the methyl ketone.

3123e: Compound 3123c (4.5 g, 14 mmol) was dissolved in CH_2Cl_2. TFA (10 mL, 13 mmol) was added dropwise and the reaction was allowed to stir for 2 h. Additional TFA (10 mL, 13 mmol) was added. After 10 min, the reaction solution was concentrated in vacuo and azeotroped with toluene (3×10 mL) to a yellow oil, which was carried on without further purification.

3123f: Hünig's base was added directly to amine 3123e (ca. 14.3 mmol), followed by EtOH (80 mL). Pyrimidine 324d, was added and the solution was heated at 90° C. for 12 h. The reaction was concentrated in vacuo, diluted with sat. aq. NH_4Cl (100 mL) and H_2O (100 mL) and extracted with EtOAc (3×200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10→100% EtOAc/hexanes) to give 5.7 g of product.

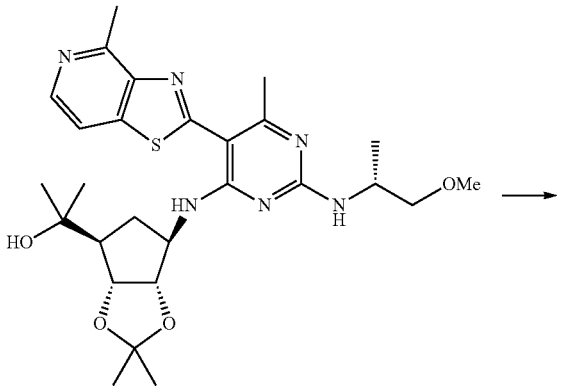
3123g: To a sealable tube was added pyridothiazole 535c (2.5 g, 17 mmol), Cs_2CO_3 (15 g, 46 mmol), CuI (1 g, 5.3 mmol), and $Pd(PPh_3)_4$ (3.2 g, 2.8 mmol). Iodide 3123f (4 g, 8.3 mmol) was dissolved in DMF (44 mL) and added to the tube, sealed, and heated to 110° C. for 1.5 h. The reaction was cooled to rt and the solution was diluted with EtOAc (400 mL) and then filtered over celite. The solution was diluted with brine (400 mL), separated, and the aqueous layer was extracted with EtOAc (2×300 mL). The combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (0→10% MeOH/CH_2Cl_2) to give 3.5 g of product.

3123h: Sulfide 3123g (6 g, 12 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0° C. mCPBA (2.9 g, 13 mmol) was added and the reaction was allowed to stir for 30 min at 0° C. The reaction was then quenched with 10% aq. $Na_2S_2O_3$ (100 mL) and sat. aq. $NaHCO_3$ (100 mL) and CH_2Cl_2 (300 mL) was added. The layers were separated and the organic layer washed with sat. aq. $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give 6.6 g of material which was carried on without further purification. The sulfoxide (4.8 g, 9.3 mmol) from the previous step was dissolved in dioxane (10 mL) and 2-methoxyethylamine (2 mL, 23 mmol) was added. The reaction was heated to 120° C. in a sealed tube for 1.5 h and then cooled to rt. The material was concentrated in vacuo and purified by flash chromatography (0→10% MeOH/CH_2Cl_2) to give 5 g of product.

3123: Acetonide 3123h (3.6 g) was dissolved in THF (24 mL) and cooled to 0° C. HCl (4N/dioxane, 24 mL) was added dropwise, followed by chilled H_2O (24 mL). The reaction was allowed to stir at rt for 7 h and quenched slowly with sat. aq. $NaHCO_3$ (60 mL). The material was filtered and washed with H_2O (10 mL), then dried under high vacuum to give 3.2 g of the product as a white solid.

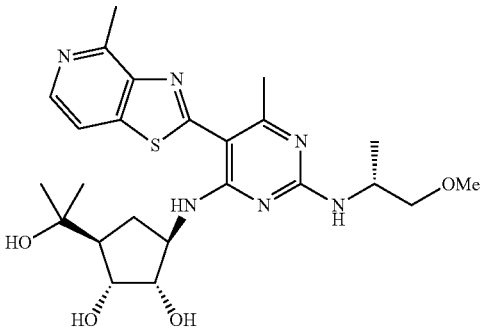
Data for 3123 h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (1H, s, br), 8.34 (1H, d, J=5.2 Hz), 7.64 (1H, d, J=5.6 Hz), 5.54 (1H, s, br), 4.68 (1H, t, J=6.4 Hz), 4.57-4.48 (2H, m), 3.74-3.69 (2H, m), 3.57 (2H, t, J=5.2 Hz), 3.38 (3H, s), 2.95 (3H, s), 2.67 (3H, s), 2.51 (1H, ddd, J=6.2, 6.2, 6.2 Hz), 2.14 (1H, ddd, J=6.2, 6.2, 6.2 Hz), 1.83-1.69 (1H, m, br), 1.69 (1H, s), 1.54 (3H, s), 1.34 (3H, s), 1.32 (3H, s), 1.24 (3H, s).

Preparation of 3137:



3137a

-continued

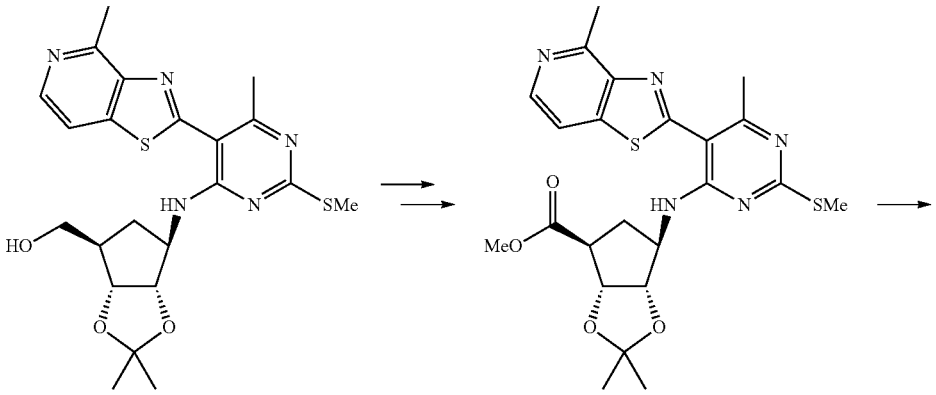


3137

Compound 3137a (prepared as described above) was converted to 3137 as reported previously for compound 3123.

Data for 3137a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (1H, s, br), 8.31 (1H, d, J=5.6 Hz), 7.62 (1H, d, J=5.6 Hz), 5.39 (1H, s, br), 4.70-4.65 (1H, m), 4.58-4.48 (2H, m), 4.44-4.36 (1H, m), 3.50-3.41 (1H, m), 3.48 (1H, dd, J=9.2, 4.4 Hz), 3.41 (1H, dd, J=9.2, 5.2 Hz), 3.38 (3H, s), 2.94 (3H, s), 2.65 (3H, s), 2.55-2.45 (1H, m), 2.14 (1H, ddd, J=6.0, 6.0, 6.0 Hz), 1.84-1.70 (1H, m, br), 1.53 (3H, s), 1.34 (3H, s), 1.31 (3H, s), 1.27 (1H, d, J=6.8 Hz), 1.24 (3H, s).

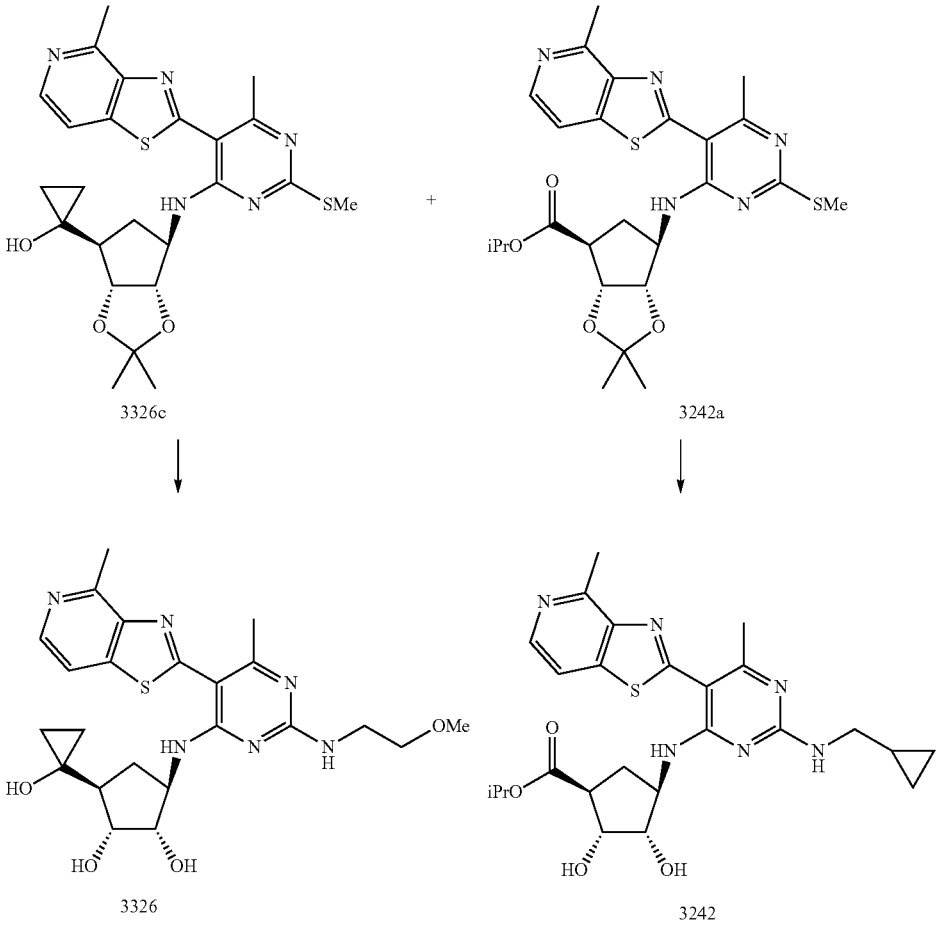
Preparation of 3226 and 3242:



3123g

3326b

-continued



3326c 3242a

3326 3242

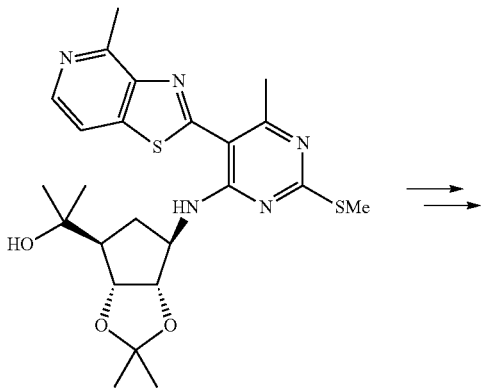
Ester 3226b was synthesized as reported for compound 3552.

3226c: Ester 3226b (460 mg, 0.9 mmol) was dissolved in THF (5 mL) and cooled to 0° C. $Ti(OiPr)_4$ (0.5 mL, 1.7 mmol) was added, followed by EtMgBr (1.3 mL, 3M/Et_2O, 3.9 mmol) as the reaction turns black. The reaction was allowed to stir overnight as bath warms to rt. The reaction was diluted with sat. aq. NH_4Cl (10 mL) and H_2O (20 mL) and EtOAc (75 mL), then filtered over celite. The layers were separated and the aqueous layer was extracted with EtOAc (75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (0→7% MeOH/CH_2Cl_2) to give 180 mg of cyclopropanol 3226c and 170 mg of isopropyl ester 3242a.

Compound 3226 was synthesized as previously reported for 3552.

Compound 3242 was synthesized as previously reported for 3552.

Preparation of 3030:



3123g

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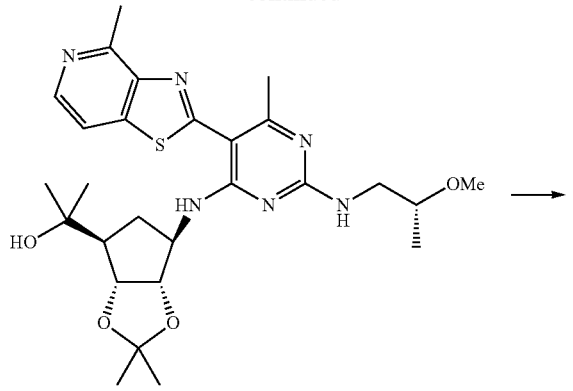
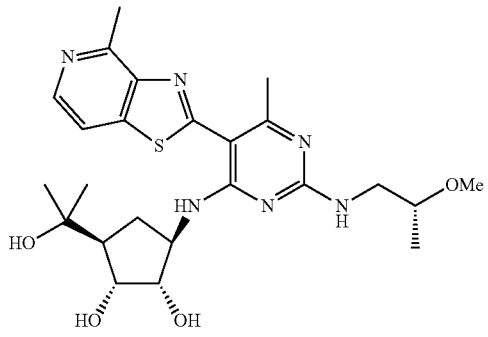


3030a

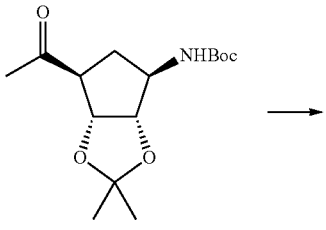


3030

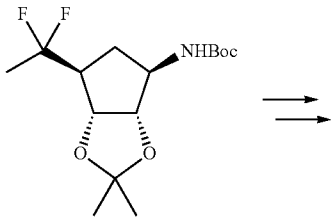
3123g (previously described above) was converted to 3030a and subsequently deprotected to 3030 using procedures described above (for 3123).

^{1}H NMR for 3030a ($CDCl_3$) δ 10.15 (1H, s, br), 8.32 (1H, d, J=5.4 Hz), 7.63 (1H, d, J=5.4 Hz), 5.55 (1H, s, br), 4.67 (1H, app. t), 4.57 (1H, m, br), 4.48 (1H, dd), 3.73-3.69 (1H, m), 3.56-3.54 (1H, m), 3.41-3.39 (1H, m), 3.38 (3H, s), 2.94 (3H, s), 2.66 (3H, s), 2.53-2.50 (1H, m), 2.15-2.13 (1H, m), 1.74 (1H, m, br), 1.54 (3H, s), 1.34 (3H, s), 1.32 (3H, s), 1.24 (3H, s), 1.20 (3H, d, J=6.3 Hz).

Preparation of 3056:



3123d



3056a

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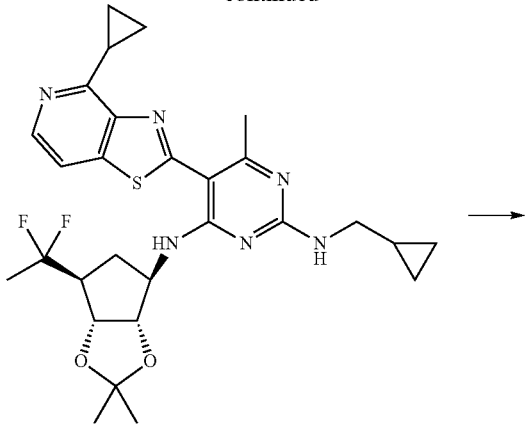
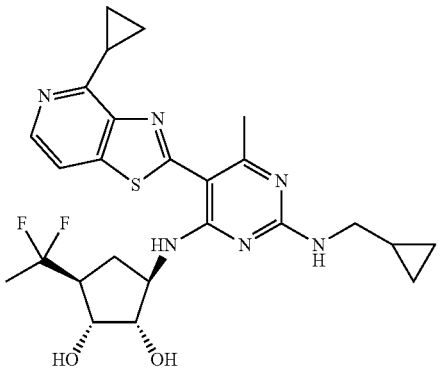


3056b



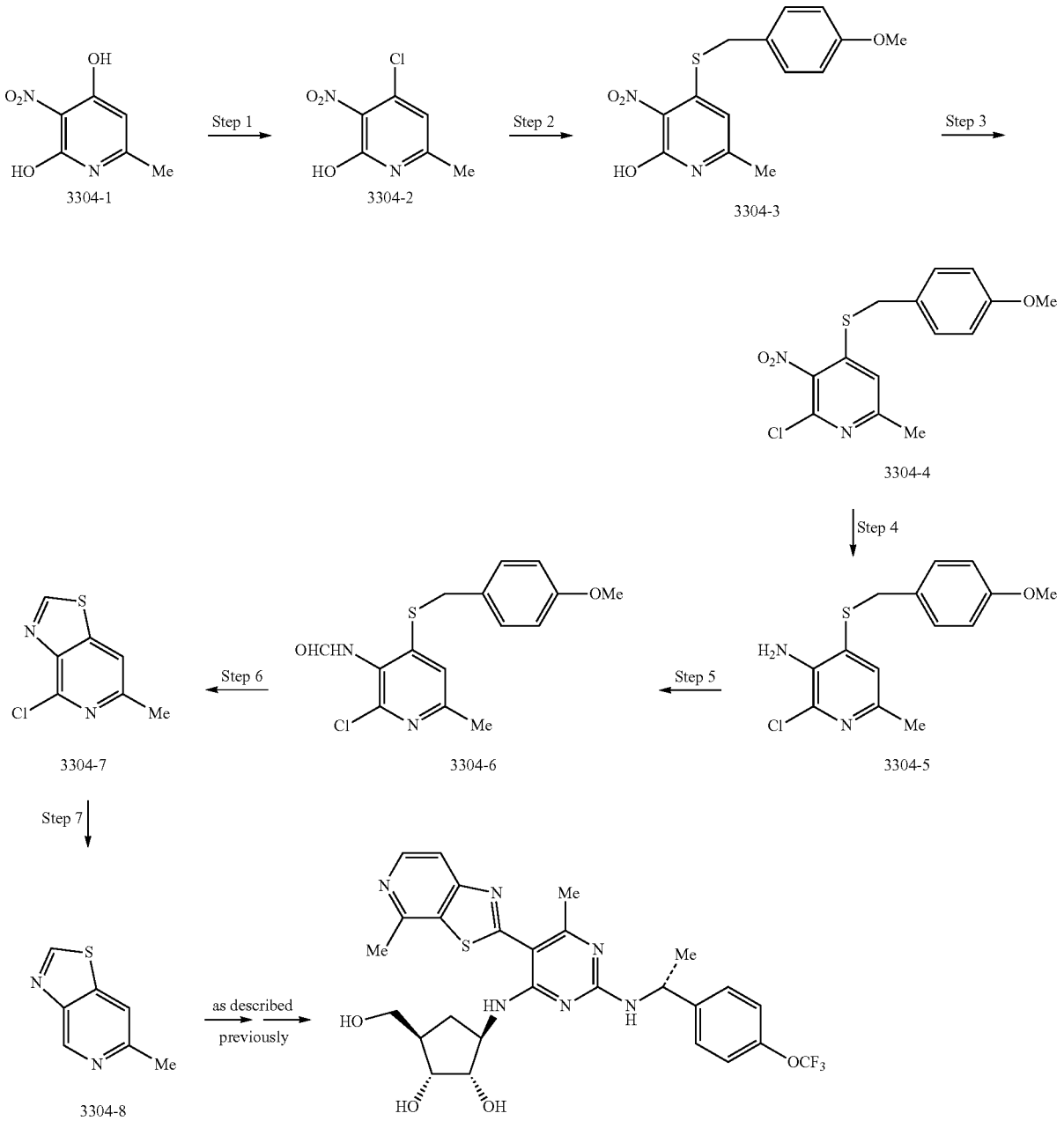
3056

To a 350 ml thick-walled glass tube was added 3123d (6 g) and Deoxo-Fluor (50% in THF, 132 ml). The tube was sealed and the solution was stirred at room temperature for 26 hrs. The reaction mixture was added dropwise to a stirred solution of saturated NaHCO3 (1440 ml). Few minutes after the addition was complete, EtOAc (1500 ml) was added, and stirred for additional 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (500 ml). The combined organic layer was dried (Na2SO4), filtered and concentrated. The residue was purified by flash chromatography (0/100 to 30/70 EtOAc/hexanes) to provide 2.74 g of 3056a.

3056a was converted to 3056b using steps described above (for 3123 h). ^{1}H NMR for 3056b ($CDCl_3$) δ 10.18 (1H, s, br), 8.30 (1H, t, J=5.4 Hz), 7.54 (1H, t, J=5.4 Hz), 5.33 (1H, s, br), 4.65 (1H, app. t, J=6.0 Hz), 4.57-4.54 (2H, m), 3.43-3.31 (2H, m), 2.91-2.85 (1H, m), 2.69 (3H, s), 2.66-2.52 (2H, m), 2.04-1.90 (2H, m), 1.67 (3H, t, J=18.9 Hz), 1.55 (3H, s), 1.30 (3H, s), 1.32-1.25 (1H, m), 1.16-1.09 (3H, m), 0.54-0.51 (2H, m), 0.28-2.25 (2H, m).

3056b was converted to 3056 using essentially procedures described above (for 3123). After completion of reaction, the mixture was concentrated (without quenching with satd NaHCO3) and dried under vacuum to provide 3056.

Preparation of 3304:



Step 1:

Using the procedures described in J. Med. Chem. 2004, 47, 5783-5790, commercially available 3304-1 was converted into the chloro-derivative 3304-2.

Step 2:

Sodium hydride (1.26 g of a 60% dispersion in mineral oil) was added to a mixture of the pyridol (3304-2; 2.7 g) and para-methoxylbenzyl thiol (2.64 g) in anhydrous THF (20 ml), under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for a period of 3 h. and the volatiles were removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic phase was separated and the aqueous phase further extracted with EtOAc (×2). The combined organic phases were dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc as eluent to give the desired sulfide (3304-3; 4.70 g), containing some impurities.

Step 3:

A mixture of the pyridine (3304-3; 11.4 g) and diethylaniline (25 ml) in phosphorous oxychloride (228 ml) was heated to reflux for a period of 3 h. After cooling, the reaction mixture was added cautiously to ice water and the slurry was stirred for a period of 2.5 h.

This mixture was extracted with EtOAc (×3) and the combined organic phases was washed with sat. aq. sodium bicarbonate, brine and dried (MgSO4). The volatiles were removed under reduced pressure. The residue was purified

by silica gel column chromatography using EtOAc:hexanes (1:3) as eluent to give the chloropyridine (3304-4; 9.00 g).

Step 4:

The chloropyridine (3304-4; 9.00 g) in ether (90 ml) was added to tin dichloride-dihydrate (63 g) in conc. aq. HCl (63 ml) and the resulting mixture was stirred at room temperature for 2 h., before adding to a mixture of EtOAc and water. The pH of the aqueous phase was adjusted to 10 using 6N aq. NaOH. The mixture was filtered through a pad of celite and the solid was thoroughly washed with EtOAc. The aqueous phase from the filtrate was separated and further extracted with EtOAc. The combined organic phases were dried (MgSO4) and the volatiles removed under reduced pressure to give the desired amine (3304-5; 7.70 g), used in the next step without purification.

Step 5:

A mixture of formic acid (2.5 ml) and acetic anhydride (5.0 ml) was heated to 60 C (oil bath temp.) under an atmosphere of nitrogen for a period of 1 h. The mixture was cooled in an ice bath and added to the amine (3304-5; 1.60 g) and the mixture stirred in an ice bath for 2 h., before partitioning between methylene chloride and sat. aq sodium bicarbonate. The aqueous phase was further extracted with methylene chloride (×2). The combined organic phases were dried (MgSO4) and the volatiles removed under reduced pressure to give the desired formamide (3304-6), used in the next step without purification.

Step 6:

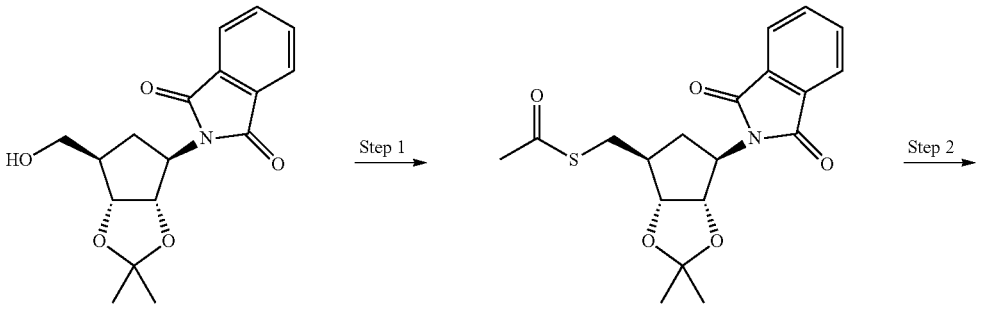
To the formamide (3304-6; all material form step 5) in trifluoroacetic acid (25 ml) was added silver tetrafluoroborate (0.212 g) and the resulting mixture was stirred at room temperature for 3 h. The volatiles were removed under reduced pressure and the residue was partitioned between sat. aq. sodium bicarbonate and methylene chloride. The aqueous phase was further extracted with methylene chloride (×2). The combined organic phases were dried (MgSO4) and volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using Cl2CH2; MeOH: 99:1 to 20:1) as eluent to give the desired pyridylthiazole (3304-7; 0.452 g).

Step 7:

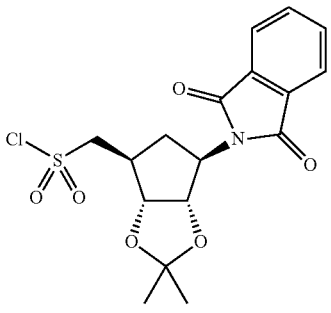
Palladium black (0.350 g) was added to a solution of the chloropyridine (3304-70.350 g) in methanol and the resulting suspension was placed under an atmosphere of hydrogen (balloon) for 72 h. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol/THF (1:1) mixture. The filtrate was concentrated under reduced pressure and the crude reaction product was purified by silica gel plate chromatography to give the desired reduced product (3304-8; 0.08 g). some starting material remained but was not pursued at this time.

3304-8 was transformed into 3304 using the procedures set forth in the previous examples.

Preparation of 3318:



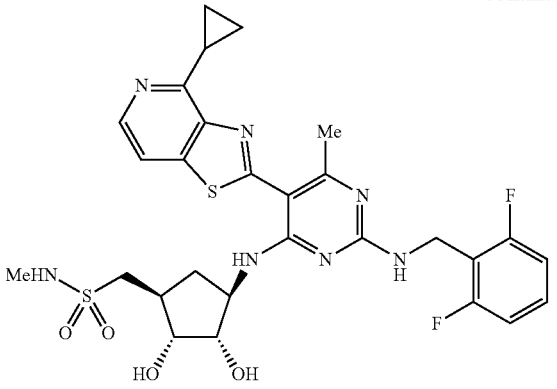
1367a 3318-1



3318-2

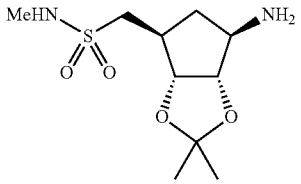
Step 3

-continued



3318

as described previously



3318-3

Step 1:

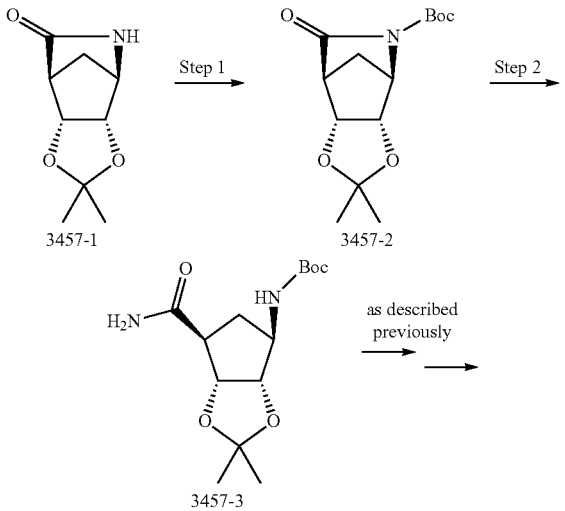
Triphenylphosphine (3.47 g) in anhydrous THF (10 ml) and cooled in an ice bath. Diisopropylazadicarboxylate (2.48 ml) was added followed by the alcohol (1367a; 2.00 g) dissolved in anhydrous THF (10 ml). Finally thiolacetic acid (1.03 ml) was added and the resulting mixture was stirred for 1 h., at 0 C. The reaction was quenched by the addition of methanol and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:10 to 1:1) as eluent to give the desired thiol ester (3318-1).

Step 2:

Sulfuryl chloride (0.508 ml) was added dropwise to a stirred mixture of the thiolacetate (3318-1; 0.958 g) and potassium nitrate (0.642 g) in anhydrous acetonitrile (30 ml) while cooled in an ice bath. The resulting mixture was stirred for a period of 30 min., before the addition of 2M methylamine in methanol (30 ml). This mixture was refluxed for a period of 2 h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using (CH2Cl2:MeOH; 99:1 to 10:1) as eluent to give the desired sulfonamide (3318-2; 0.152 g).

3318-2 was transformed into 3318 using the procedures set forth in the previous examples.

Preparation of 3457:

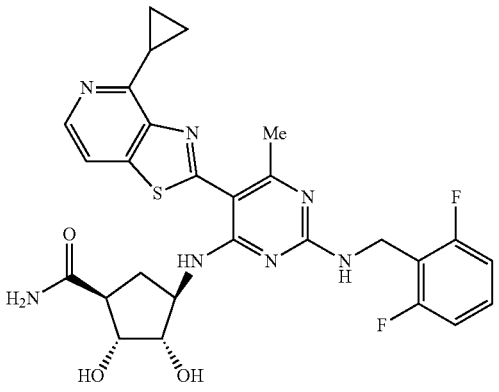


3457-1

3457-2

3457-3

-continued



3457

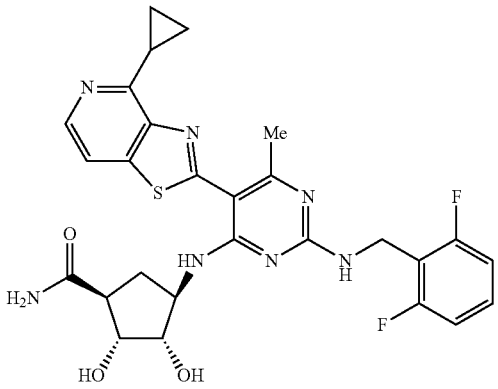
Step 1:

DMAP (6.66 g) was added to a stirred mixture of the lactam (3457-1; 10.00 g) and di-tertbutyldicarbonate (23.84 g) in anhydrous THF (200 ml) and the resulting mixture stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using EtOAc; hexanes (1:5) to give the desired (3457-2; 14.8 g).

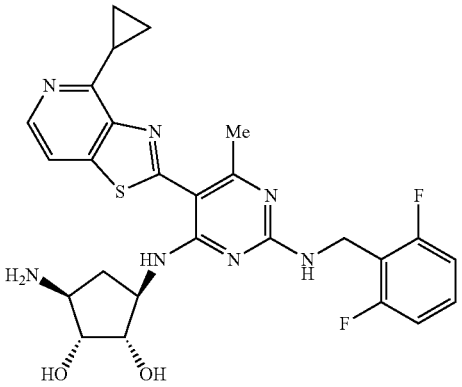
Step 2:

Ammonia was bubbled through a solution of the lactam (3457-2; 2.00 g) in dioxane (10 ml) in a sealed tube. The tube was sealed and heated to 100 C for 1 h. After cooling, the volatiles were removed under reduced pressure to give the desired amide (3457-3; 2.00 g).

3457-3 was transformed into 3457 using the procedures set forth in the previous examples.



3457

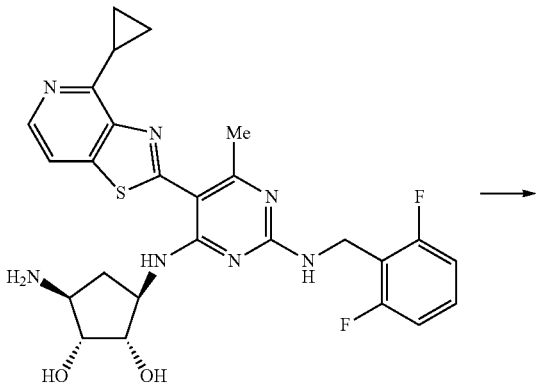


3458

Preparation of 3458:

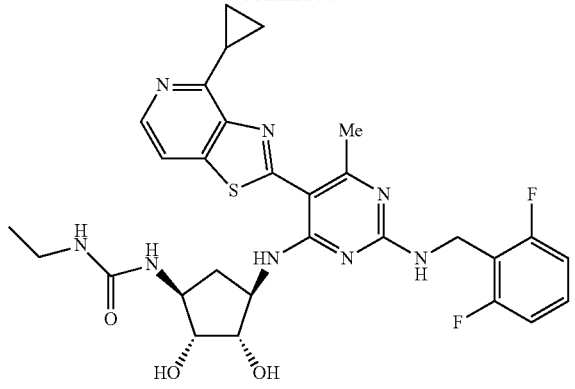
[Bis(trifluoroacetoxy)iodo]benzene (0.163 g) was dissolved in acetonitrile/water (1:1) (2 ml) and added to the amide (3457; 0.200 g) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was partitioned between methylene chloride and sat. aq, sodium bicarbonate. The aqueous phase was separated and further extracted with methylene chloride (×2). The combined organic phases were dried, dried (MgSO4) and the volatiles removed under reduced pressure. The residue was purified by silica gel plate chromatography to give the desired amine (3458; 0.093 g).

Preparation of 3459:



3458

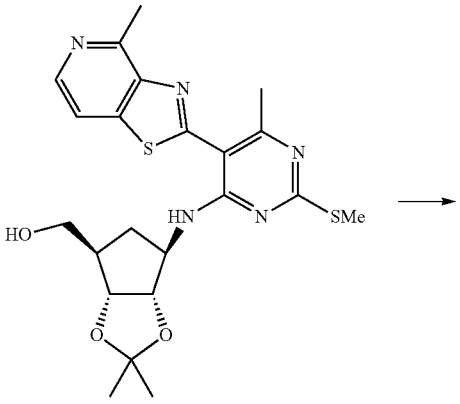
-continued



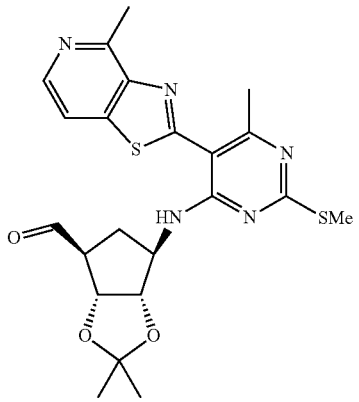
3459

Ethyl isocyanate (0.0065 g) in anhydrous methylene chloride (2 ml) was added to the amine (3458; 0.053 g) and the resulting mixture was stirred at room temperature, overnight. The volatiles were removed under reduced pressure and the residue was purified by silica gel plate chromatography using (CH_2Cl_2; MeOH; 20:1) to give the desired urea (3459; 0.039 g).

Preparation of 3825:



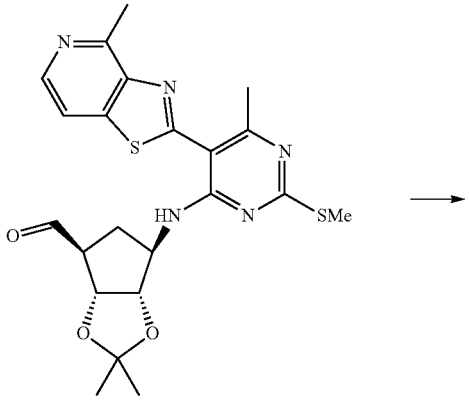
535d



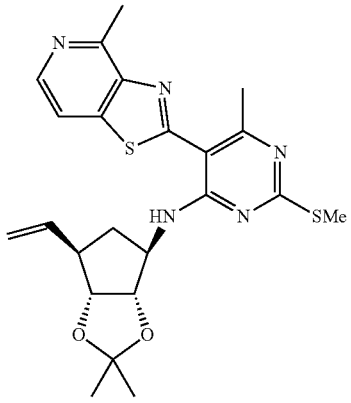
1398b

A mixture of alcohol (535d, 2.0 g, 4.22 mmol) and iodobenzene diacetate (1.2 eq, 1.63 g) was dissolved in dichloromethane (42 mL) and treated with TEMPO (10 mol %, 66 mg). The mixture was stirred overnight. The mixture

was diluted with ethyl acetate (200 mL) and washed with aq sodium bicarbonate (50 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Redisep (120 g) silica gel column (gradient: 0 to 70% THF in hexanes) to give the product (1398b, 1.0 g, 50%) as a yellow solid.

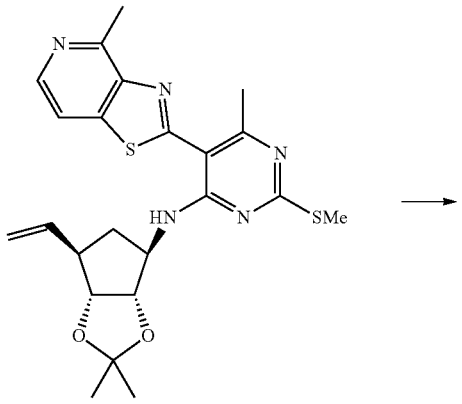


1398b

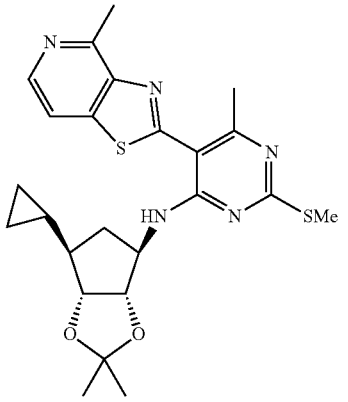


3825a

A suspension of methyltriphenylphosphonium bromide (2.3 eq, 1.74 g) in dry THF (20 mL) was placed in an ice-water bath and n-butyllithium was added dropwise (2.25 eq, 1.90 mL of 2.5 M soln in hexanes). The resulting yellow solution was stirred for 10 min followed by slow addition (over 5 min) of a solution of aldehyde 1398b (1.00 g, 2.12 mmol) in dry THF (20 mL). The reaction mixture was stirred at 0° C. until all starting material was consumed. After 30 min TLC (5% methanol in DCM) showed a complete reaction. The reaction was quenched by addition of half-saturated ammonium chloride (50 mL) and the product was extracted into ethyl acetate (100 mL). Upon separation the organic layer was washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a Redisep (80 g) silica gel column (gradient: 0 to 30% solvent B in DCM (solvent B: 20% methanol in DCM)) to give the product (960 mg, 96%) as a yellow foam. TLC (50% THF in hexanes) showed a major impurity. The product was adsorbed on silica gel and purified on a Redisep (80 g) silica gel column (gradient: 0 to 40% THF in hexanes) to give the product (3285a, 560 mg, 57%) as a slightly yellow foam.

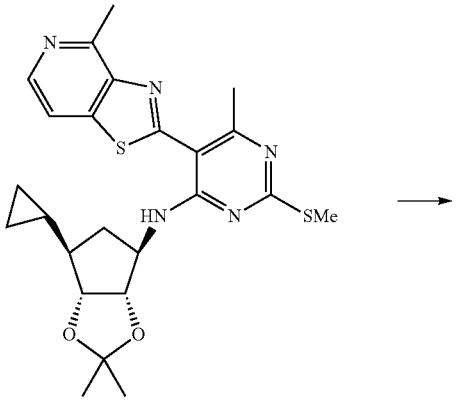


3825a

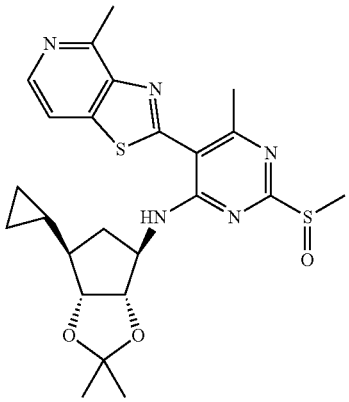


3285b

A round-bottom flask was charged with dry DCM (4 mL) under anhydrous conditions and placed in an ice-water bath followed by addition of diethyl zinc (10.0 eq, 9.79 mL of 1 M soln in heptane). A solution of TFA (10.0 eq, 0.750 mL, d 1.480) in dichloromethane (2 mL) was added and the mixture was stirred for 10 min followed by addition of a solution of diiodomethane (10.0 eq, 0.787 mL, d 3.325) in dry DCM (2 mL). The mixture was stirred for 10 min and a solution of alkene 3285a (460 mg, 0.979 mmol) in DCM (5 mL) was added dropwise. The reaction mixture was stirred at 0° C. and monitored by LCMS analysis of quenched aliquots. After 5 h some starting material remained. The reaction was quenched by addition of sodium bicarbonate (20 mL) and the product was taken into ethyl acetate (2×30 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a Redisep (40 g) silica gel column (gradient: 0 to 40% THF in hexanes) to give the product (3285b, 169 mg, 36%) as a white powder.

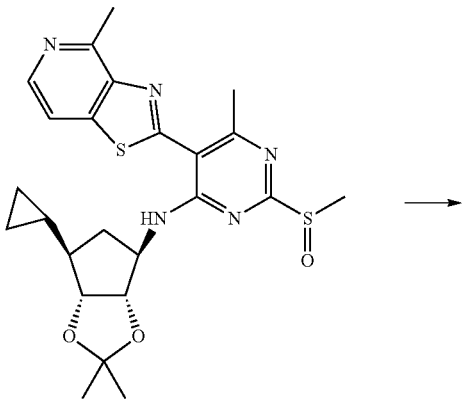


3285b



3285c

A solution of methyl sulfide (3285b, 169 mg, 0.349 mmol) in 7 mL of THF was placed in an ice-water bath and treated with m-CPBA (1.05 eq, 84 mg of 75% m-CPBA). The reaction mixture was stirred for 2 h. The reaction was diluted with ethyl acetate (50 mL) and washed with aqueous saturated sodium bicarbonate soln (10 mL), 10% aqueous sodium thiosulfate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to give the crude product (3285c, ~99%, 172 mg) as a slightly yellow powder which was used without further purification.



3285c

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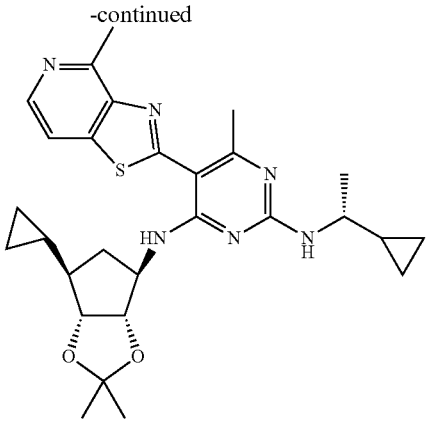
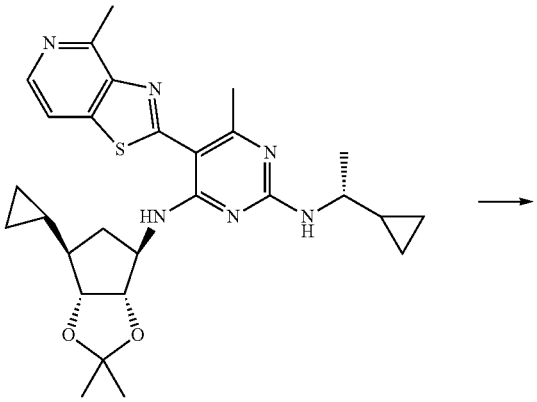
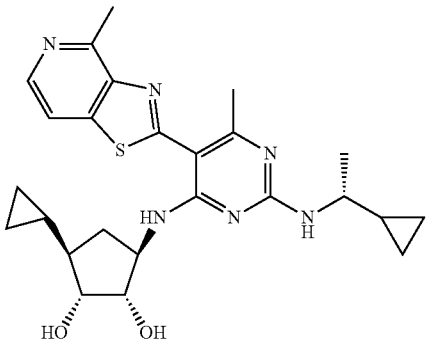


3285d

A reaction tube was charged with a solution of sulfoxide 3285c (86 mg, 0.172 mmol) in dioxane (2 mL) and (R)-1-cyclopropylethanamine (0.25 mL). The tube was sealed and heated in an oil bath at 105° C. for 2 h. The mixture was concentrated in rotavap and the residue was purified on a Redisep (24 g) silica gel column (gradient: 0 to 40% THF in hexanes) to give the product (3285d, 80 mg, 90%) as a white powder.



3285d

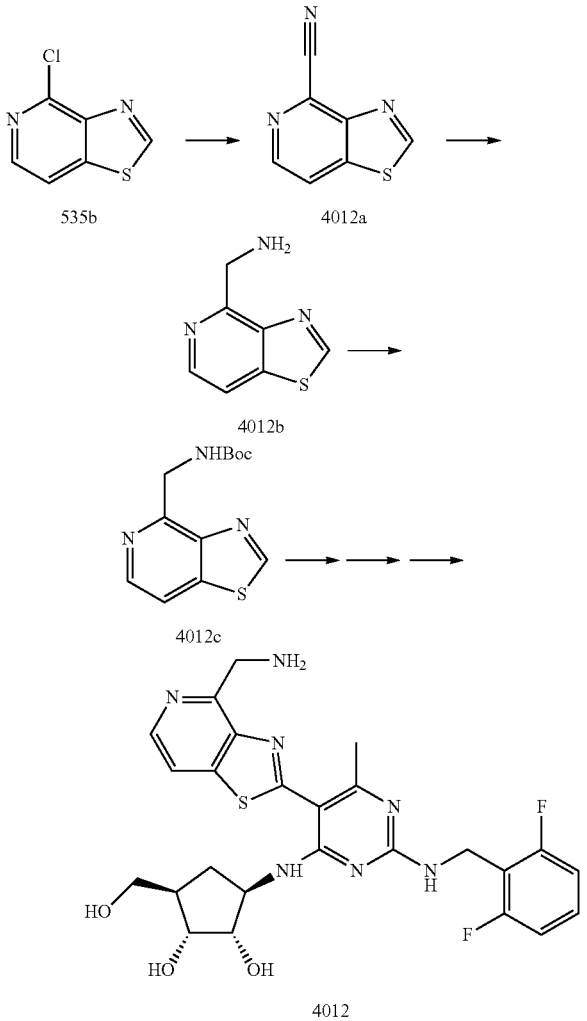


3285

A solution of acetonide 3285d (75 mg, 0.144 mmol) in 4 mL of 1:1 THF/MeOH was treated with 4 M HCl solution in dioxane (2 mL) and water (1 drop). The reaction was

stirred at room temp and monitored by LCMS. After 2 h, only 60% conversion was achieved. More water (4 drops) was added and a complete reaction was achieved after 2 h. The mixture was concentrated to dryness in rotavap and dried under vacuum. The dry residue was dissolved in MeOH (1 mL) and the product was triturated with ethyl acetate (5 mL). The mixture was concentrated in rotavap to give an off-white solid. The solids were washed with ethyl acetate (2×3 mL) to give the product (3285, 72 mg, 93%) as an off-white powder.

Preparation of 4012:



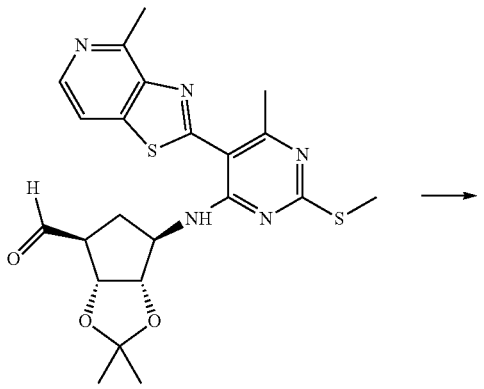
Step A: A solution of 535b (3.1 g, 18.169 mmol) in anhydrous dimethylformamide (60 ml) was treated with zinc cyanide (2.13 g, 18.169 mmol) and triphenylphosphine (47 mg, 0.1816 mmol) under argon. The mixture was heated to 85° C., then treated with tetrakis(triphenylphosphine)palladium(0) (2.3 g, 1.99 mmol) and continued heating for 12 hours. The mixture was cooled to room temperature followed by the addition of ethyl acetate and filtration of undissolved solids. The ethyl acetate filtrate was washed with water, brine and filtered through sodium sulfate. The solvent was evaporated and the residue was purified on silica gel with 0-50% ethyl acetate/hexanes gradient to give compound 4012a, (1.05 g).

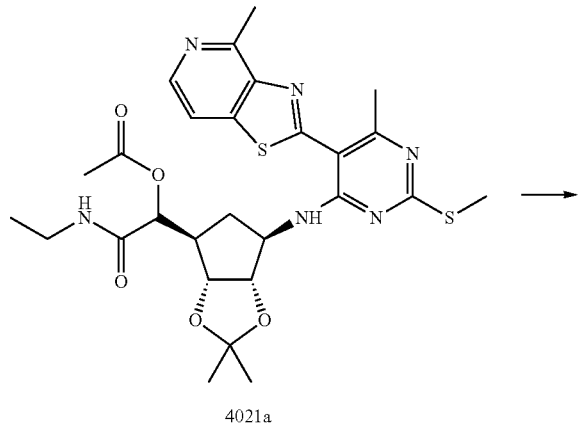
Step B: A solution of 4012a (900 mg, 5.583 mmol) in acetic acid (80 ml) was treated with palladium hydroxide on carbon (900 mg) and hydrogen gas @ 50 psi for 4 hours. The catalyst was filtered off through celite and solvent was removed by evaporation to give crude 4012b as a crystalline solid, (1.76 g).

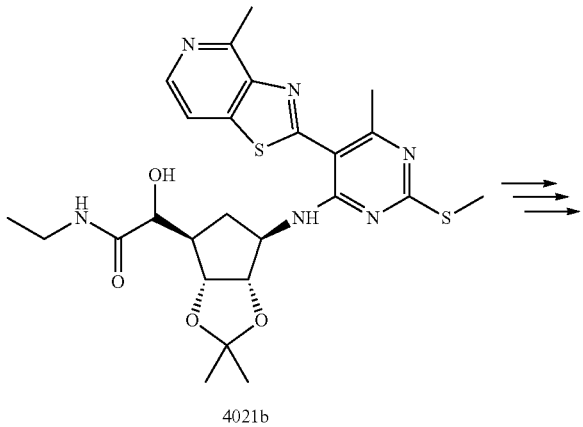
Step C: A slurry of crude 4012b (1.76 g) in acetonitrile (10 ml) and dichloromethane (10 ml) was treated with triethylamine (2.33 ml, 16.75 mmol) and boc anhydride (1.218 g, 5.583 mmol) then stirred at room temperature for 3 hours. The solvent was removed to dryness and the residue was purified on silica gel with 0-60% ethyl acetate/hexanes gradient to give 4012c as an off white solid, (1.0 g).

Compound 4012 was prepared from 4012c as described earlier.

Preparation of 4020 and 4021:







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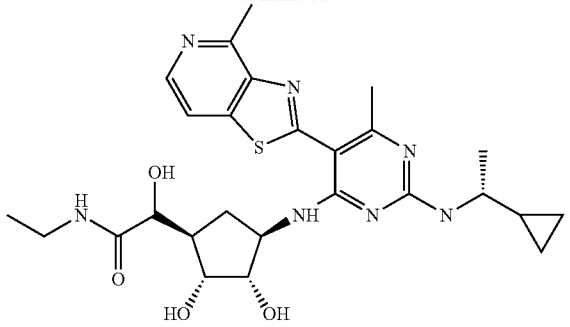


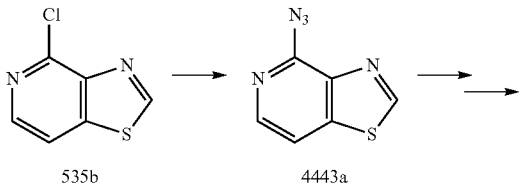
4020 and 4021

Step A: A solution of aldehyde 1398b (350 mg, 0.7421 mmol) (prepared as in a previously described example) in dichloromethane (5 ml) was treated with acetic acid (84.9 ul, 1.484 mmol) and isocyanoethane (81.7 mg, 1.484 mmol) then stirred at room temperature for 20 hours. The solvent was evaporated to dryness and the residue was purified on silica gel with 0-60% acetone/dichloromethane gradient to give compound 4021a as a yellow solid in 79% yield.

Step B: A solution of acetate 4021a (345 mg, 0.588 mmol) in tetrahydrofuran (1 ml), methanol (1 ml) and water (1 ml) was treated with lithium hydroxide (28.1 mg, 1.176 mmol) and stirred at room temperature for 3 hours. The solvent was evaporated to dryness and the residue was purified on silica gel with 0-100% acetone/dichloromethane gradient to give compound 4021b (211 mg) as an off white solid in 66% yield.

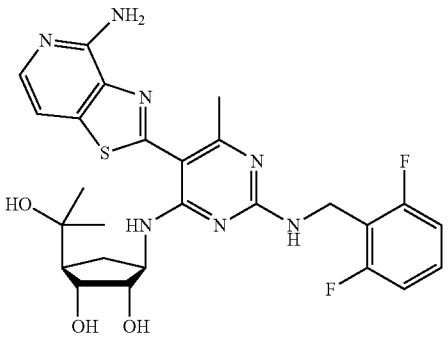
4021b was converted to the final targets as described in a previously example. The isomers were separated on a reverse phase C18 column to give 4020 and 4021 as single diastereomers.

Preparation of 4443:



535b

4443a

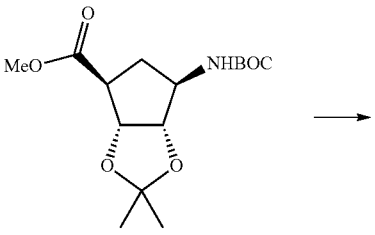


4443

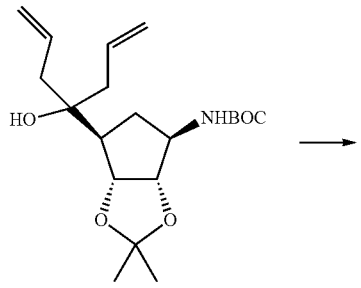
Compound 535b (800 mg, 4.69 mmol) and NaN_3 (1.52 g, 23.4 mmol) were mixed with 5 ml DMF. The reaction mixture was heated at 120° C. for 18 h. The mixture was cooled down to room temperature and filtered. The solid was collected and mixed with 15 ml of water. The suspension was filtered and the solid was collected to give compound 4443a (0.36 g) as light yellow solid.

The product 4443 was synthesized from 4443a using previously described procedures.

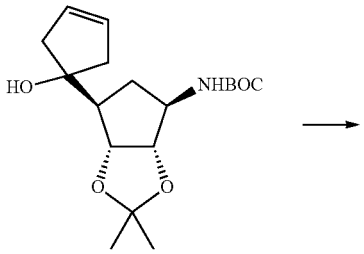
Preparation of 4534:



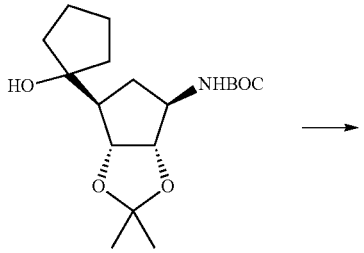
3123b



4534a



4534b



4534c

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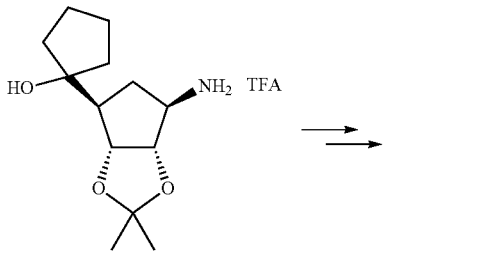
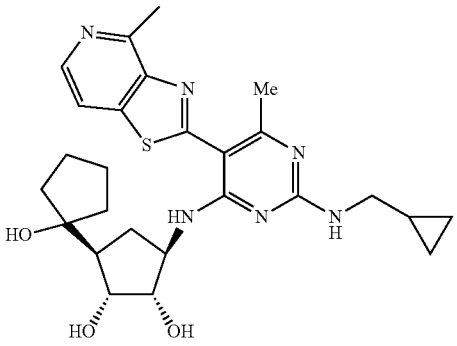


4534d



4534

Step 1:

Compound 3123b (1.6 g, 5.1 mmol) was dissolved in THF (60 mL) and the solution was cooled to 0° C. Allyl magnesium bromide (25.5 mmol, 25.5 mL, 1 M solution in THF) was added dropwise at the temperature and the mixture was stirred at 0° C. to 25° C. for 18 h. After quenched by aqueous NH_4Cl solution, the organic layers were extracted by CH_2Cl_2 and the combined organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to afford a crude compound 4534a (1.9 g), which was used for the next step without further purification.

Step 2:

Compound 4534a (1.9 g, 5.1 mmol) was dissolved in CH_2Cl_2 (60 mL) and treated with Grubbs 2nd generation catalyst (219 mg, 0.25 mmol) at 25° C. After stirred for 18 h, the reaction mixture was filtered through a celite pad and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, gradient) to afford a pure compound 4534b (1.2 g).

Step 3:

Compound 4534b (1.2 g, 3.54 mmol) was dissolved in MeOH (60 mL) and treated with 10% Pd/C under H_2 pressure (45 psi). After 18 h at 25° C., the mixture was filtered through a celite pad and the filtrate was concentrated in vacuo to afford compound 4534c (1.2 g).

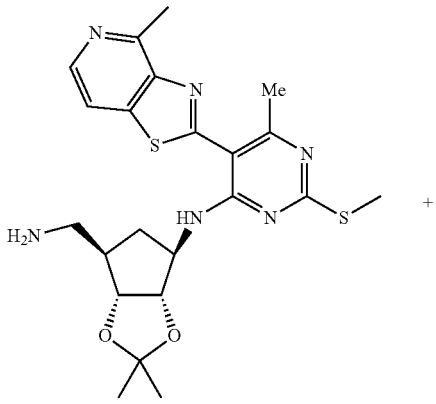
Step 4:

Compound 4534c (1.2 g, 3.51 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0° C. Trifluoroacetic acid (4.5 mL) was added to the solution and the mixture was stirred at 0° C. to 25° C. for 18 h. The mixture was concentrated in vacuo to afford a crude compound 4534d (~1.0 g), which was used for the next step without further purification.

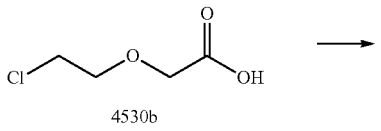
Step 5:

The product 4534 was synthesized from 4534e using procedures described earlier.

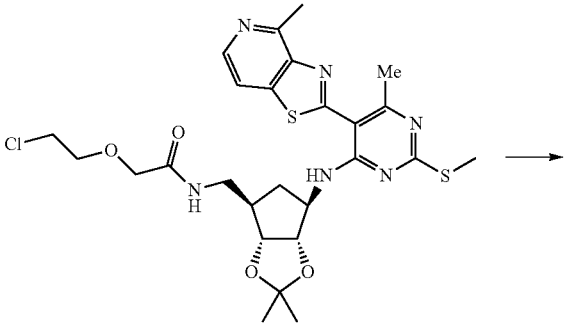
Preparation of 4530:



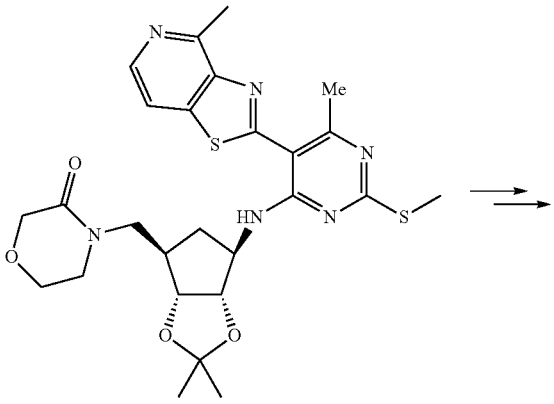
4530a



4530b



4530c



4530d

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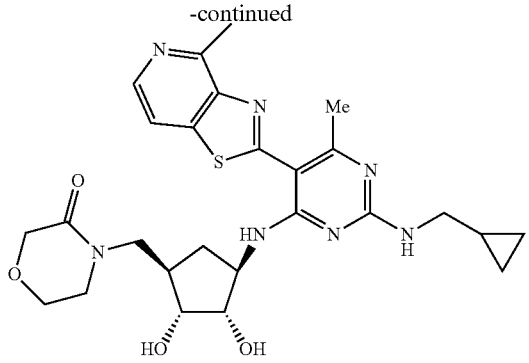


4530

Step 1:

Compounds 4530a (490 mg, 1.03 mmol) and 4530b (0.15 mL, 1.24 mmol) were dissolved in CH_2Cl_2 (10 mL)—CH_3CN (5 mL) at 0° C. EDCl (238 mg, 1.24 mmol) and DMAP (13.5 mg, 0.11 mmol) were added to the solution and the mixture was stirred at 0° C. to 25° C. for 18 h. The mixture was added to aqueous $NaHCO_3$ solution and the organic layers were extracted by CH_2Cl_2 and the combined organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2 to 8% MeOH in CH_2Cl_2, gradient) to afford a pure compound 4530c (484 mg).

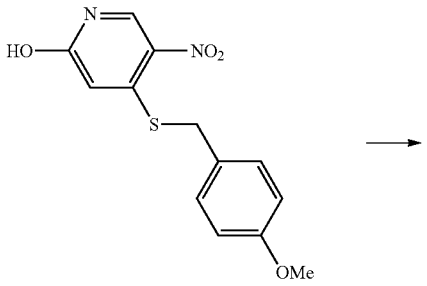
Step 2:

Compound 4530c (484 mg, 0.82 mmol) was dissolved in CH_3CN (10 mL)-DMF (4 mL) and treated with K_2CO_3 (136 mg, 0.99 mmol). After stirred at 100° C. for 3 days, The mixture was added to ice-water and the organic layers were extracted by EtOAc and the combined organic solution was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2 to 8% MeOH in CH_2Cl_2, gradient) to afford a pure compound 4530d (356 mg).

Step 3:

The product 4530 was synthesized from 4530d using procedures described above.

Preparation of 4942:



4942Aa

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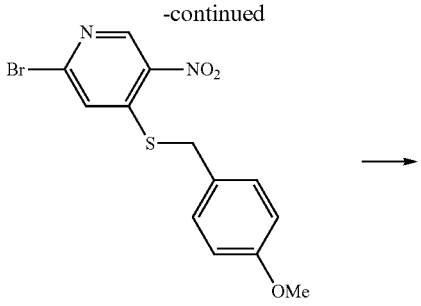
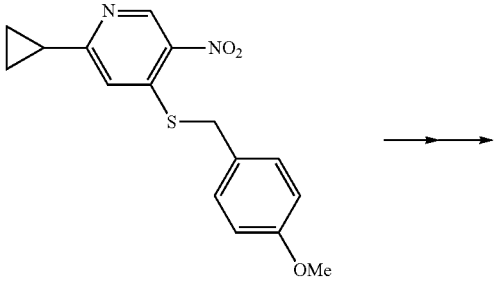
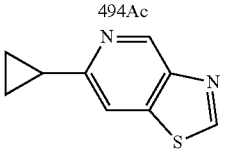


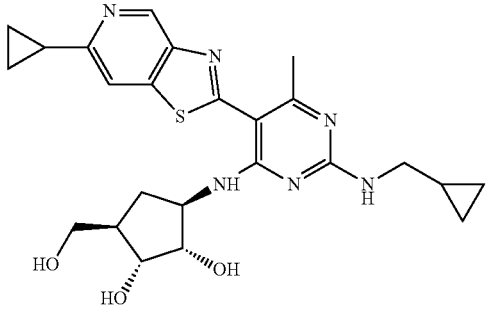
4942Ab



494Ac



4942A



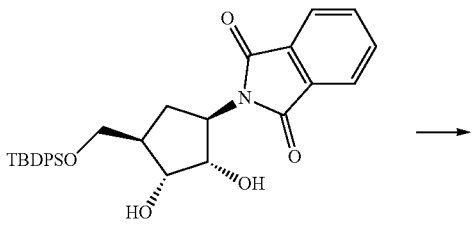
4942

To a solution of compound 4942Aa (3.4 g, 11.6 mmol) in toluene (15 mL) was added $POBr_3$ (11 g, 38.4 mmol), and the whole heated at 100° C. for 3 h. The reaction mixture was then allowed to cool to RT and then was poured into ice water, neutralized with K_2CO_3, and extracted with EtOAc. The EtOAc layer was washed with brine, dried, and evaporated to give 4942Ab (2.75 g).

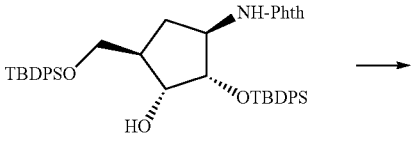
Compound 4942Ab (200 mg, 0.57 mmol), cyclopropylzinc bromide (1.7 mL, 0.86 mmol), and tetrakis[triphenylphosphine]palladium (0) (100 mg) were heated for 2.6 h at 86° C. The reaction mixture was then cooled to RT, and water and EtOAc were added. The EtOAc layer was removed, and the water layer again extracted with EtOAc. The EtOAc layers were combined, washed with brine, evaporated, and purified by silica gel column chromatograph eluting with 9:1 cyclohexane/EtOAc to give 4942Ac (74 mg, 42%). The conversion of 4942Ac to 4942A was essentially the same as with the preparation of 6-Me-pyridothiazole (described in Preparation of 3304), that is described earlier. The coupling of 4942A and subsequent conversion of

the resulting adduct to a target such as 4942 is essentially the same as with the preparation of other pyridothiazole-containing targets.

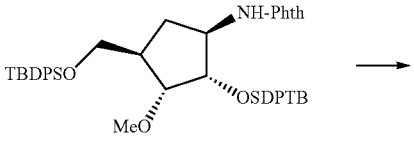
Preparation of 4905:



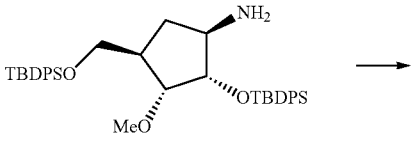
4905A



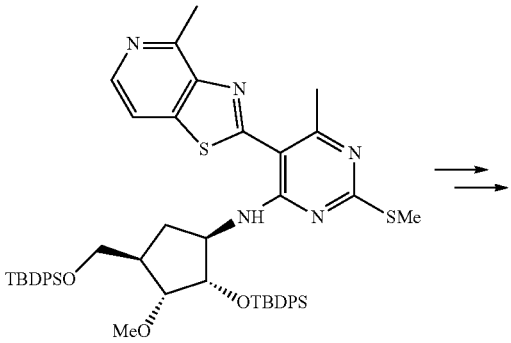
4905B



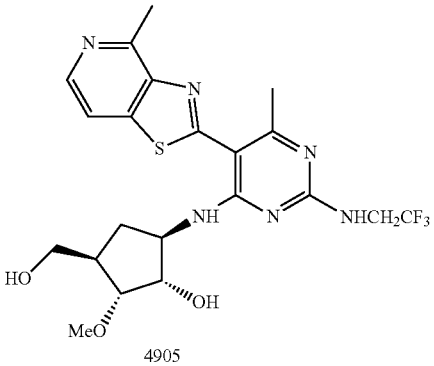
4905C



4905D



4905E



4905

Phth = phthalimide

To a solution of 4905A (2.5 g, 4.85 mmol) was added pyridine (1.76 mL), followed by solid $AgNO_3$ (999.1 mg (5.82 mmol). The mixture was sonicated and stirred to facilitate partial dissolution. After ~10 min, TBDPS-Cl was added dropwise by syringe to the stiffed mixture over ~10 min. The reaction mixture was stiffed at RT for 20.5 h and then filtered. The collected solid was washed with CH_2Cl_2, the filtrate plus washes were diluted with more CH_2Cl_2 and then transferred to a separatory funnel. This solution was washed with cold saturated $NaHCO_3$ (pH~8), water, and brine. The organic layer was then dried over $MgSO_4$ and evaporated to an off-white foam (4.45 g). Flash column chromatography eluting with a 0-90% gradient of cyclohexane/$CHCl_3$ gave the desired intermediate 4905B in 76% yield (2.78 g) along with some starting material (57.4 mg) and the corresponding 2'-OH (3'-O-protected) product (477 mg, 13%).

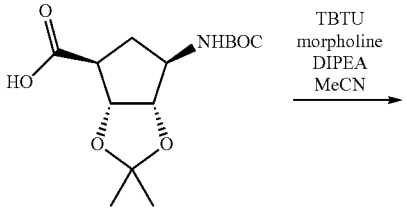
To an argon-flushed pressure tube (~120 mL capacity) was added DTBMP (7.42 g, 35.4 mmol) and 4905B (1.78 g, 2.36 mmol). CH_2Cl_2 (18 mL) was then added, the mixture was stiffed, and methyl triflate (3.4 mL, 29.5 mmol) was added by syringe. The tube was again flushed with argon, tightly sealed, and placed into a preheated 90° C. oil bath for 10 h, then allowed to cool to RT overnight. The reaction mixture was then poured into cold saturated $NaHCO_3$ (~125 mL) with vigorous stirring. This mixture was stirred at RT for 1 h, EtOAc (~150 mL) was added, and after ~5 min more stirring, it was transferred to a separatory funnel. The organic layer was isolated and washed with water and brine. Drying with $MgSO_4$ followed by evaporation gave an off-white slurry (8.83 g after drying). Flash column chromatography, eluting with a gradient of 0-10% EtOAc/hexane gave 4905C (1.63 g, 90%).

Intermediate 4905C (2.55 g, 3.32 mmol) was added to hot EtOH (50 mL), and the resulting cloudy solution was treated in one portion with hydrazine hydrate (2.47 mL, 49.9 mmol). The reaction flask was then equipped with a reflux condenser and the mixture heated in a preheated 90° C. oil bath. After 15 min, a white solid began forming. After 5 h, the reaction mixture was a thick slurry. The reaction mixture was removed from the oil bath, and the mixture stiffed at RT overnight. The white solid was then collected, washed with EtOH, and the EtOH filtrate evaporated to a white solid (2.22 g). Flash column chromatography of this solid eluting with $CHCl_3$ and then 99:1 $CHCl_3$/7N NH_3 in MeOH then gave 2.3 g of 4905D.

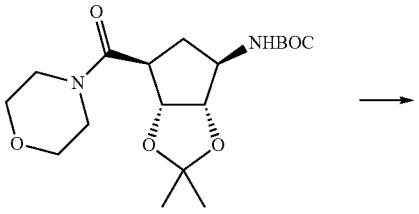
Conversion of 4905D to 4905E followed analogous procedures presented earlier.

Solid Et_4NF (50 mg, 0.333 mmol) was added in one portion to a solution of 4905E in MeCN in a 15 mL pressure reaction tube. The tightly sealed tube was placed into a preheated 85° C. oil bath for 3 h. The reaction mixture was evaporated to a yellow semisolid 118.9 mg which was then purified by prep TLC (Analtech GF plated) developed 4 times in 9:1 $CHCl_3$/MeOH+1% NH_4OH. The product-containing bands from the multiple plates were extracted with MeOH containing a few drops of NH_4OH. The washes were evaporated to a white solid which was then added to boiling MeCN, and a few drops of water added to clarify. When the solution was allowed to slowly cool to RT, little material came out of solution, and so the mixture was concentrated to ~5 mL and then refrigerated overnight. The resulting white solid was collected, washed with cold MeCN, dried in vacuo to give 4905 (25.6 mg, 77%).

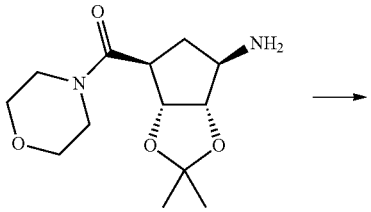
Preparation of 4923:



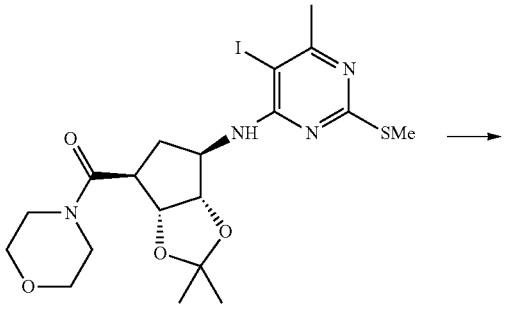
4923A



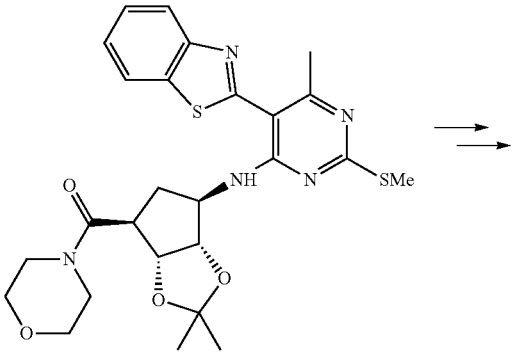
4923B



4923C



4923D



4923E

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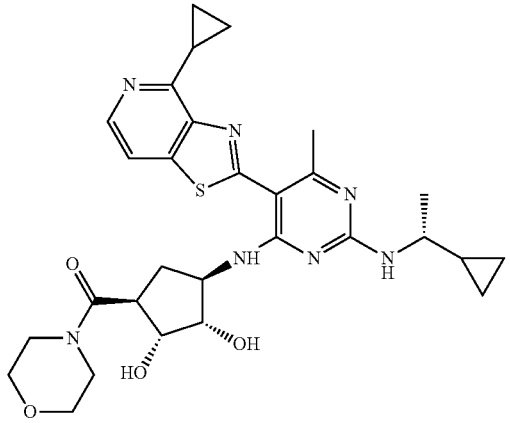


4923

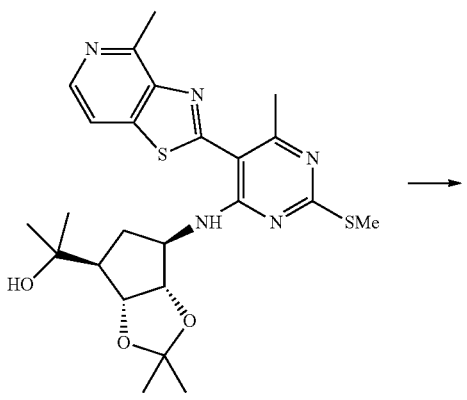
Compound 4923A (0.5 g, 1.65 mmol) was added to MeCN (5 mL) and treated with TBTU (0.6 g, 1.86 mmol) at RT with stirring under argon. Morpholine (0.16 mL, 1.8 mmol) and DIPEA (0.32 mL) in MeCN (5 mL) was added, and the reaction mixture was stiffed at RT overnight. The reaction mixture was then concentrated to dryness, preadsorbed onto silica, and purified by column chromatography, eluting with 0-30% EtOAc/$CHCl_3$, giving 4923B (0.456 g).

BOC-protected 4923B (2.3 g, 6.21 mmol) was added slowly to TFA with stirring at RT. After 1.5 h, the reaction mixture was concentrated to dryness and co-evaporated with toluene (2×25 mL) to give 4923C, which was used without further purification.

Conversion of 4923C to provide 4923D, followed by introduction of the 5-heterocycle to afford 4923E was performed by the same procedures described previously.

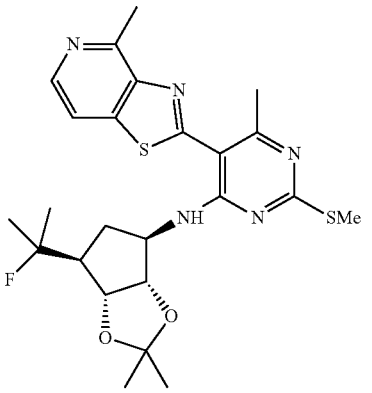
Replacement of the 2-SMe of 4923E with the α-methylcyclopropylmethylamine followed by removal of the isopropylidine protecting group to give target compound 4923 was performed by the same procedures described previously.

Preparation of 4954:



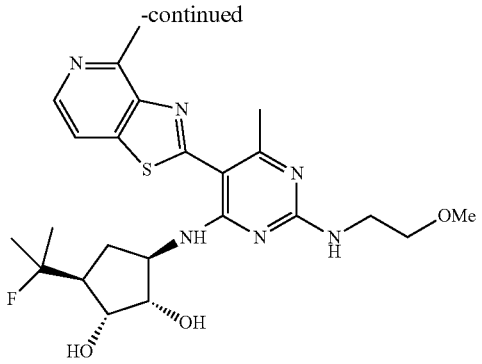
4954A

-continued

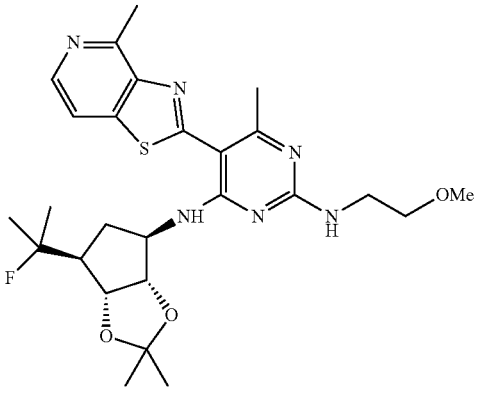


4954B

-continued



4954

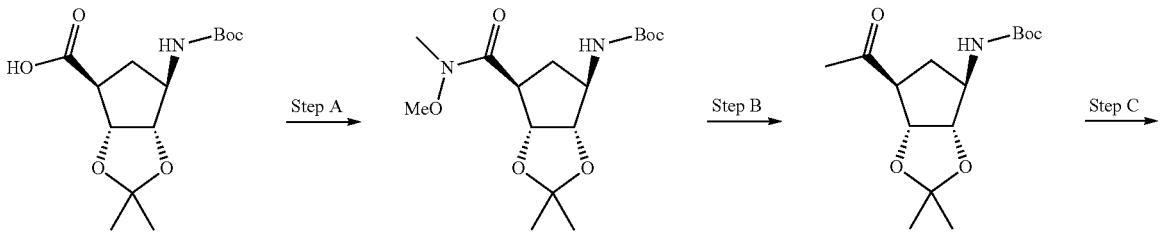


4954C

To a solution of 4954A (860 mg, 1.71 mmol) in anhydrous CH_2Cl_2 at 0-5° C. was added dropwise (syringe) 50% Deoxo-Fluor in THF (1.46 mL, 3.43 mmol) over 14 min. The yellow solution was stirred at 0-5° C., and after 1.5 h, only a trace of Im-23 was present (by TLC). After 2 h at 0-5° C., cold saturated $NaHCO_3$ was added, and then solid $NaHCO_3$ was added in small portions until bubbling ceased. The solution as diluted with CH_2Cl_2, stirring at 5° C. was continued for ~0.5 h. The mixture was then transferred to a separatory funnel, shaken and the layers were separated. The aqueous layer was extracted with portions of CH_2Cl_2 until the organic layer remained essentially colorless. The organic layers were combined, washed with water (×2) dried ($MgSO_4$), evaporated to a light orange solid (840 mg). Chromatographic purification of this solid using an ISCO chromatography system (ISCO Gold cartridge) eluting with a 0-20% acetone/cyclohexane gradient gave 4954B (79 mg).

Conversion of 4954B to 4954C followed analogous procedures presented earlier. Aqueous 1N HCl was added in one portion at RT to a suspension of 4954C (87.4 mg, 0.165 mmol) in MeOH resulting in complete dissolution. The reaction mixture was stirred at RT for 33 h, and after TLC showed the reaction was complete, the solution was evaporated to a small volume. Since the solution was still acidic, it was diluted with MeOH, stirred for 3.5 h, and then evaporated to dryness. The residue was coevaporated 2× with MeOH to give a pale yellow solid (468 mg). Flash column chromatography on silica gel eluting with a gradient of 0-5% MeOH/$CHCl_3$ gave 4954 (74.8 mg).

Preparation of 5036:

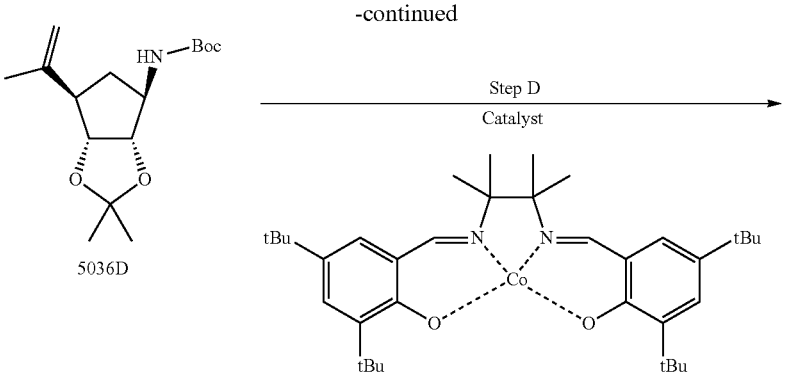


5036A

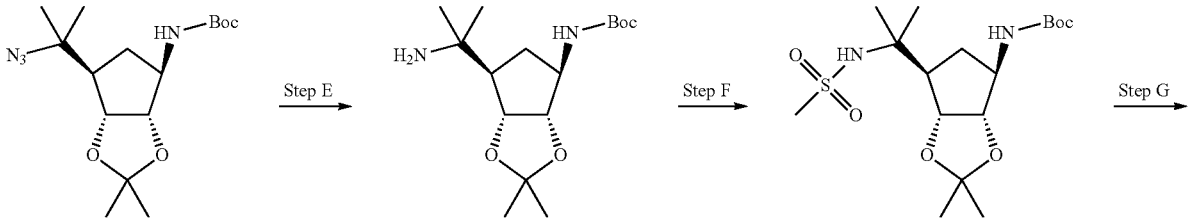
5036B

5036C

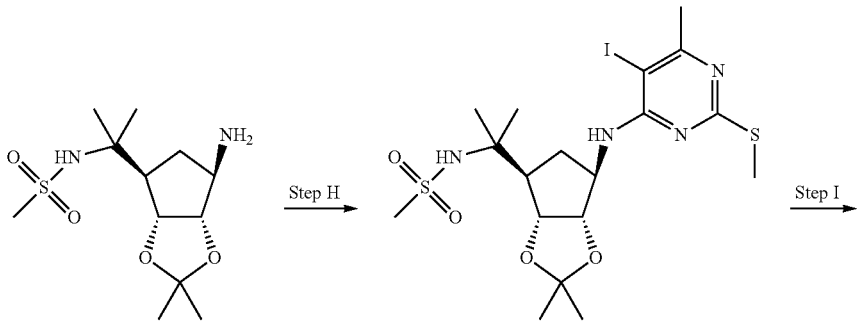
-continued



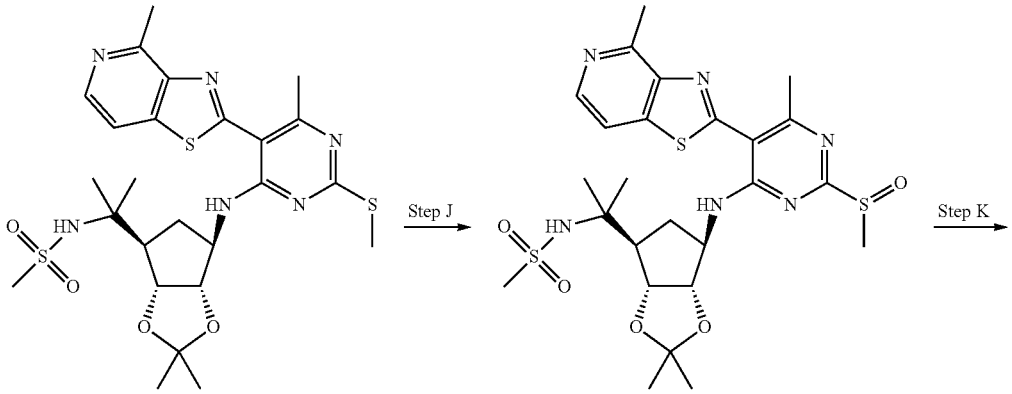
5036D



5036E 5036F 5036G

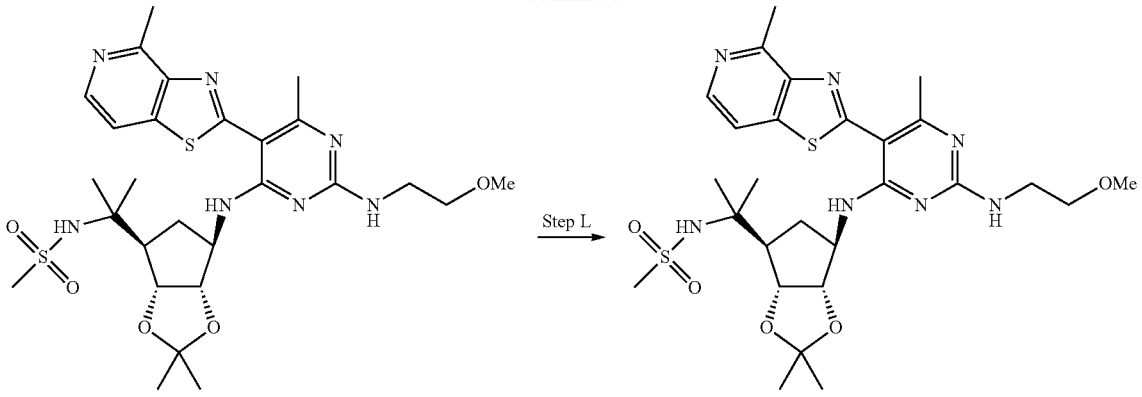


5036H 5036I



5051J 5051K

-continued



5036L 5036

Step A:

Compound 5036A (15.0 g, 50 mmol), EDC (11.4 g, 60 mmol), HOBt (9.5 g, 70 mmol), N,O-dimethylhydroxylamine hydrochloride (7.27 g, 75 mmol), and triethylamine (21 mL, 150 mmol) were stirred overnight in methylene chloride (250 mL). The reaction was quenched with water and the organic layer was washed with saturated sodium bicarbonate, dried over sodium sulfate and concentrated. Column chromatography (1:1 hexanes/ethyl acetate) provided 5036B (13.5 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.15 (m, 1H), 4.7 (m, 1H), 4.45 (m, 1H), 4.15 (m, 1H), 3.7 (s, 3H), 3.4 (m, 1H), 3.2 (s, 3H), 2.5 (m, 1H), 1.8 (m, 1H), 1.45 (s, 3H), 1.4 (s, 9H), 1.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 155.3, 110.8, 87.2, 84.0, 78.9, 61.6, 56.6, 47.7, 32.3, 32.1, 28.5, 26.7, 24.4.

HRMS (ESI): calcd for C16H28N2O6 (M+H) 345.2020 Found 345.2025.

Step B:

Compound 5036B (2.3 g, 6.66 mmol) was dissolved in THF (100 mL) and cooled in an ice bath. A 3M solution of MeMgBr in ether (13.3 mL, 40 mmol) was added dropwise and the reaction was stirred at rt until no starting material was present by TLC. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. Column chromatography (2:1 hexanes/ethyl acetate) provided 5036C (1.8 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.2 (bs, 1H), 4.75 (m, 1H), 4.4 (m, 1H), 4.1 (m, 1H), 3.15 (m, 1H), 2.35 (m, 1H), 2.25 (s, 3H), 1.85 (m, 1H), 1.45 (s, 3H), 1.4 (s, 9H), 1.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.5, 155.5, 111.3, 86.4, 82.0, 58.8, 56.8, 30.9, 29.3, 28.4, 26.7, 24.4.

HRMS (ESI): calcd for C15H25NO5 (M+H) 300.1805 Found 300.1808.

Step C

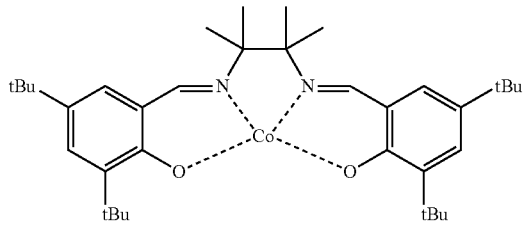
Methyltriphenylphosphonium bromide (29.2 g, 84 mmol) was suspended in THF (300 mL) and treated with 0.5M potassium hexamethyldisilazide (160 mL). After 30 minutes a solution of compound 5036C (10.0 g, 33.35 mmol) in THF (100 mL) was added dropwise. The reaction was stirred for 3 hours and then quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by column chromatography (3:1 hexanes/ethyl acetate) to provide 5036D (7.0 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7 (s, 1H), 4.6 (s, 1H), 4.35 (t, J=6.25 Hz, 1H), 4.28-4.2 (m, 1H), 3.82-3.74 (m, 1H), 2.45-2.38 (m, 1H), 2.2-2.1 (m, 1H), 1.6 (s, 3H), 1.52-1.42 (m, 1H), 1.35 (s, 3H), 1.3 (s, 9H), 1.1 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 145.4, 112.6, 110.2, 85.6, 82.9, 79.5, 57.0, 50.6, 35.3, 28.3, 27.3, 24.9, 21.7.

HRMS (ESI): calcd for C16H27NO4 (M+H) 298.2013 Found 298.2015.

Catalyst:



Catalyst

The catalyst was synthesized as described in Gaspar, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* 2008, 47(31), 5758-5760.

Step D:

Compound 5036D (18 mg, 0.03 mmol) was dissolved in ethanol (2 mL) and then treated sequentially with compound 3 (300 mg, 1 mmol) dissolved in ethanol (8 mL), tosylazide (497 mg, 2.5 mmol), and phenylsilane (0.16 mL, 1.3 mmol). The reaction was allowed to stir at room temperature for 1.5 hours and was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound 5036E as a colorless oil (275 mg, 81%).

^{1}H NMR (CD_3OD, 400 MHz) δ 4.45 (t, ^{3}J=6.8 Hz, 1H), 4.25 (t, ^{3}J=6.2 Hz, 1H), 3.8 (m, 1H), 2.1 (m, 1H), 2.0 (m, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.36 (s, 3H), 1.3 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (CD_3OD, 100 MHz) δ 156.5, 112.9, 84.6, 79.6, 78.7, 61.4, 56.2, 52.9, 32.6, 27.2, 26.4, 23.9, 23.7, 23.6.

HRMS (ESI): calcd for C16H28N4O4 (M+H) 341.2183 Found 341.2182.

Step E:

Compound 5036E (2.0 g, 5.5 mmol) was dissolved in methanol (30 mL) and treated with CuSO4 pentahydrate (200 mg) in an ice bath. The reaction was treated with sodium borohydride (400 mg, 11 mmol) slowly and then stirred for 1 hour. The reaction was quenched with brine and ethyl acetate. The two layers were passed through a celite plug and then the organic layer was dried over sodium sulfate and concentrated. Isolated 1.4 g of 5036F that was used without purification.

Step F:

Compound 5036F (800 mg, 2.53 mmol) was dissolved in methylene chloride (10 mL) and treated with triethylamine (0.5 mL). Methanesulfonyl chloride (292 mg, 2.53 mmol) was added dropwise and the reaction was stiffed for 1 hr followed by quenching with water. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (1:1 hexanes/ethyl acetate) provided compound 5036G (530 mg).

Step G:

Compound 5036G (530 mg, 1.34 mmol) was dissolved in methylene chloride (5 mL) and treated with TFA (1 mL). After one hour the solvent was removed and then the residue was treated with methylene chloride and 1M sodium hydroxide. The organic layer was dried over sodium sulfate and concentrated to provide 5036H that was used without purification (380 mg).

Step H:

Reaction was performed in a similar manner to Procedure U, Step 1.

[M+H]=557.0

Step 1:

Reaction was performed in a similar manner to Procedure Z, Step 4.

[M+H]=579.25

Step J:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=595.25

Step K:

Reaction was performed in a similar manner to Procedure Z, Step 5.

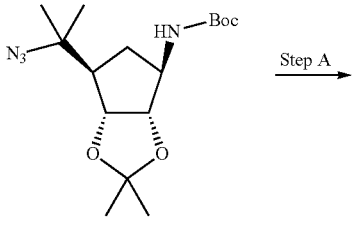
[M+H]=606.2

Step L:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=566.3

Preparation of 5051:



5036E

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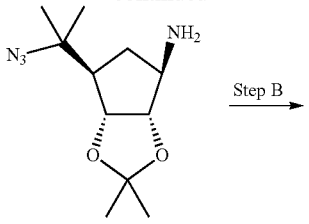
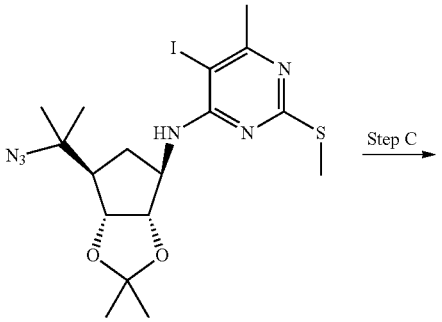
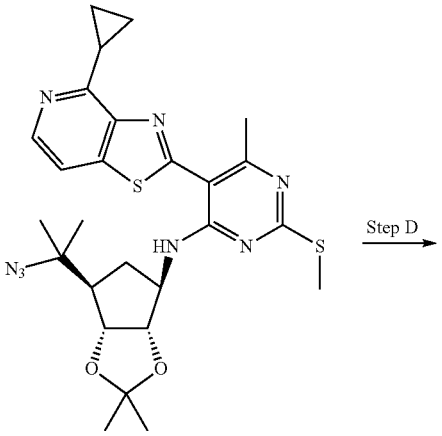


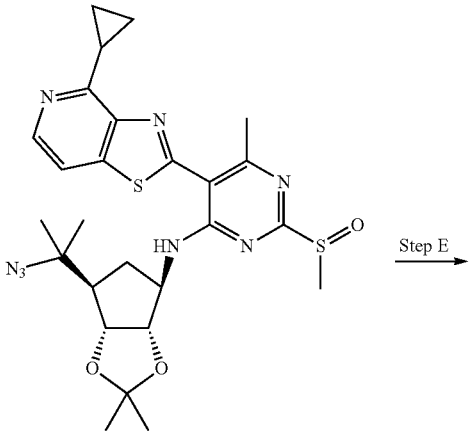
5051B



5051C



5051D



5051E

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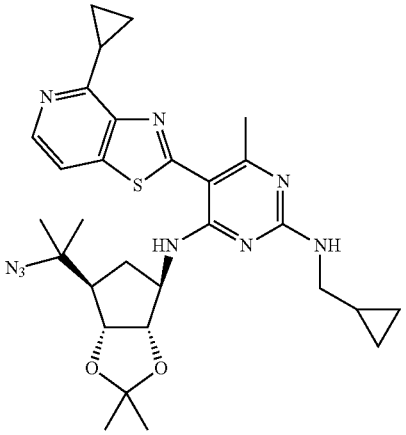
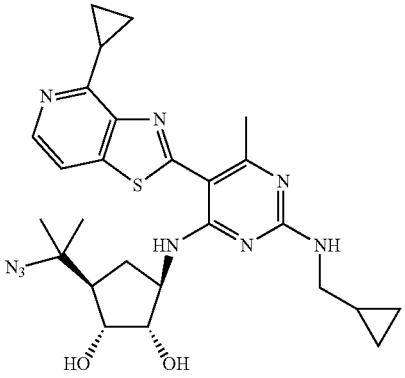


5051E

Step F



5051

Step A:

Compound 5051A (500 mg, 1.37 mmol) was dissolved in methylene chloride (5 mL) and treated with TFA (1 mL). After one hour the solvent was removed and then the residue was treated with methylene chloride and 1M sodium hydroxide. The organic layer was dried over sodium sulfate and concentrated to provide 5051B that was used without purification (380 mg).

Step B:

Reaction was performed in a similar manner to Procedure U, Step 1.

[M+H]=505.0

Step C:

Reaction was performed in a similar manner to Procedure Z, Step 4.

[M+H]=553.29

Step D:

Reaction was performed in a similar manner to Procedure Z, Step 5.

[M+H]=569.28

Step E:

Reaction was performed in a similar manner to Procedure Z, Step 5.

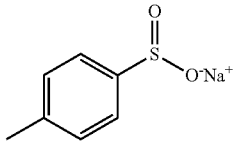
[M+H]=576.41

Step F:

Reaction was performed in a similar manner to Procedure Z, Step 5.

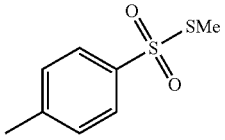
[M+H]=536.2

Preparation of 5062:

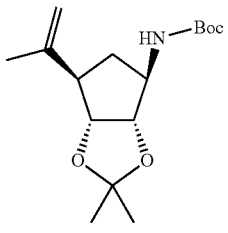


5062A

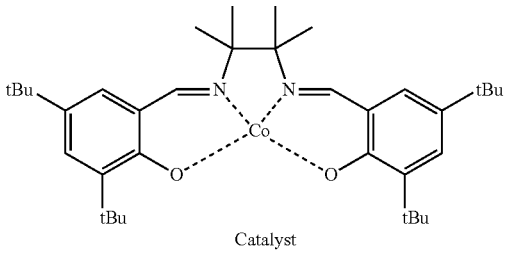
Step A



5062B



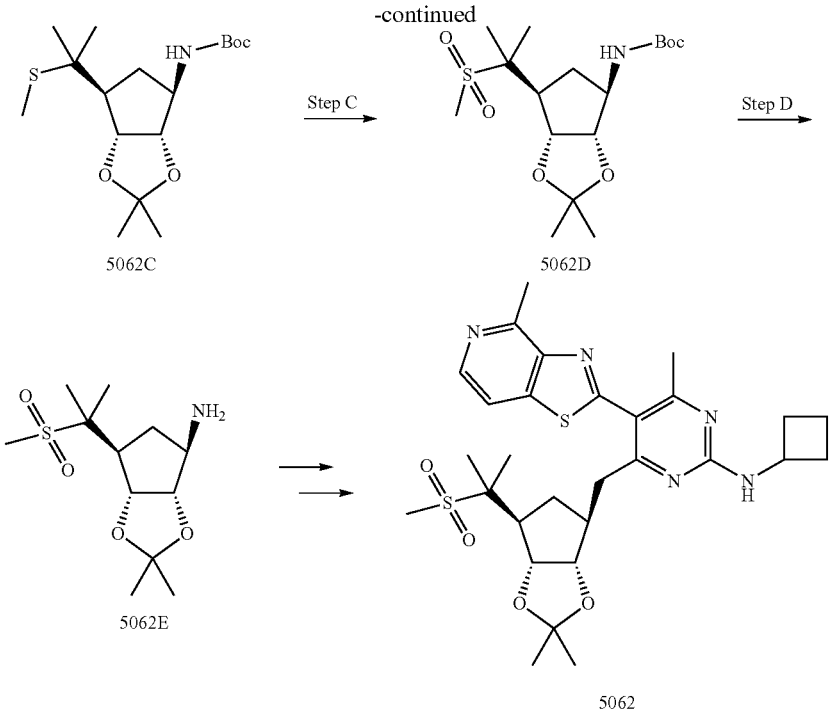
5036D



Catalyst

Step B

-continued



Step A:

Sodium 4-methylbenzenesulfinate (compound 5062A) (10.0 g, 56 mmol), dimethyldisulfide (1.59 g, 17 mmol), and iodine (8.06 g, 32 mmol) were dissolved in methylene chloride (200 mL) and stirred for 5 hours. The reaction was quenched with 10% aqueous sodium thiosulfate and extracted with methylene chloride. The organic layer was dried over sodium sulfate and concentrated. Column chromatography (20:1 hexanes/ethyl acetate) provided compound 5062B as a yellow solid (4.39 g, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.8 (d, ^{3}J=8.5 Hz, 2H), 7.34 (d, ^{3}J=8.3 Hz, 2H), 2.48 (s, 3H), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 129.9, 127.1, 21.6, 18.1.

HRMS (ESI): calcd for C8H10O2S2 (M+H) 203.0195 Found 203.0194.

Step B:

Catalyst (synthesized as described in 5036) (18 mg, 0.03 mmol) was dissolved in ethanol (2 mL) and then treated sequentially with compound 5036D (300 mg, 1 mmol) dissolved in ethanol (8 mL), compound 5062B (3 mmol), and phenylsilane (0.16 mL, 1.3 mmol). The reaction was allowed to stir at room temperature for 1.5 hours and was quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. Column chromatography (4:1 hexanes/ethyl acetate) provided compound 5062B (310 mg, 90%) as a thick colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.8 (bs, 1H, N—H), 4.5 (t, J=6.25 Hz, 1H), 4.2 (t, J=7.03 Hz 1H), 3.8 (m, 1H), 2.25 (m, 1H), 2.1 (m, 1H), 2.0 (s, 3H), 1.6-1.5 (m, 1H), 1.45 (s, 3H), 1.38 (s, 9H), 1.21 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.4, 113.0, 84.8, 80.0, 79.2, 57.0, 53.0, 44.8, 33.6, 28.4, 27.6, 26.7, 26.4, 25.2, 10.8.

HRMS (ESI): calcd for C17H31NO4S (M+H) 346.2047 Found 346.2048.

Step C:

Compound 5062C (160 mg, 0.465 mmol) was dissolved in methylene chloride (8 mL) and treated with 77% m-CPBA (259 mg, 1.16 mmol). After stirring at room temperature for 2 hours the reaction mixture was washed with 1M potassium carbonate solution, dried over sodium sulfate and concentrated. Column chromatography (2:1 ethyl acetate/hexanes) provided compound 5062D (173 mg, 99%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95 (bs, 1H, N—H), 4.5 (m, 1H), 4.35 (m, 1H), 3.8 (m, 1H), 2.8 (s, 3H), 2.4 (m, 2H), 1.65 (m, 1H), 1.45 (s, 3H), 1.4 (s, 3H), 1.38 (s, 9H), 1.33 (s, 3H), 1.23 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.5, 84.0, 79.6, 79.4, 62.6, 56.5, 48.0, 35.5, 34.0, 28.3, 27.5, 25.2, 21.0, 18.5.

HRMS (ESI): calcd for C17H31NO6S (M+H) 378.1945 Found 378.1945.

Step D:

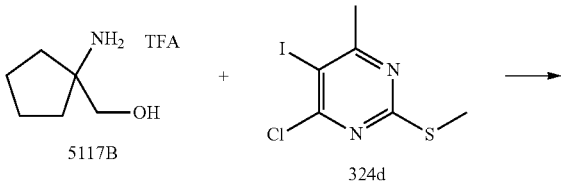
Compound 5062D (500 mg, 1.37 mmol) was dissolved in methylene chloride (5 mL) and treated with TFA (1 mL). After one hour the solvent was removed and then the residue was treated with methylene chloride and 1M sodium hydroxide. The organic layer was dried over sodium sulfate and concentrated to provide 5062E that was used without purification (380 mg).

Compound 5062 was synthesized from 5062E using general procedures U and Z.

Preparation of 5117:

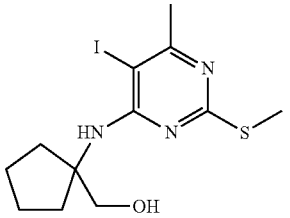
5117A 5117B

In a 200 mL round bottom flask 5117A (13.953 mmol) was dissolved in dichloromethane and then treated with trifluoroacetic acid (5 mL). Reaction mixture was stirred at room temperature for 21 hrs and then concentrated, to afford 5117B as a brown oil in quantitative yield.



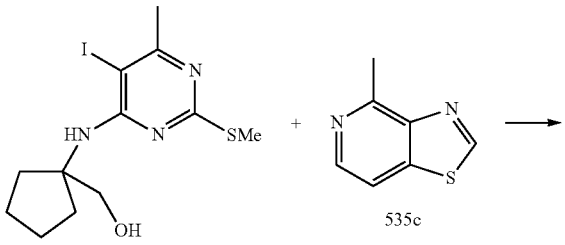
5117B

324d



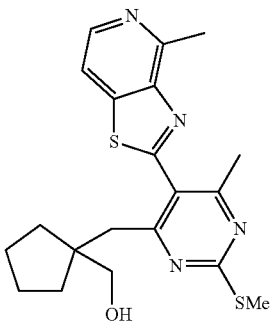
5117C

In a 200 mL round bottom flask 5117B (13.953 mmol), 324d (27.907 mmol) and N,N-Diisopropylethylamine (69.765 mmol) were suspended in ethanol and refluxed at 90° C. for 48 hrs. Reaction mixture was poured onto ice water and extracted with ethyl acetate. Organic portions were then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purified by silica gel column to afford 5117C as a white solid in quantitative yield.



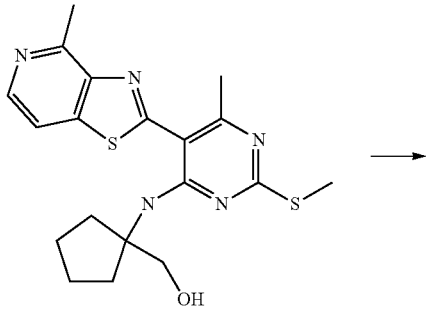
5117C

535c

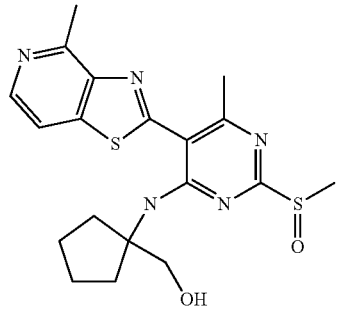


5117D

In a 20 mL Biotage microwave vial 5117C (0.7915 mmol), 535c (0.9498 mmol), copper (I) iodide (0.3957 mmol), cesium carbonate (3.9575 mmol) and tetrakis(triphenylphosphine) palladium (0.1583 mmol) were suspended in DMF and irradiated in microwave at 100° C. for 30 min Reaction mixture was then filtered through celite, and filtrate was washed with water and extracted with ethyl acetate. Organic portions were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Purified by silica gel column to 5117D 79% yield.

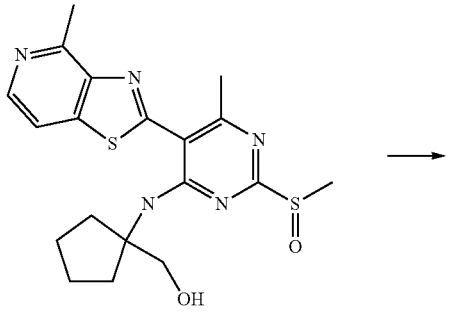


5117D



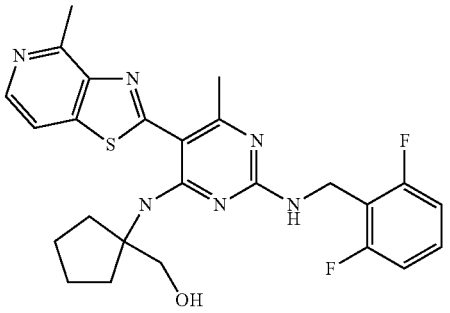
5117E

In a 125 mL round bottom flask 5117D (0.6234 mmol) was dissolved in dichloromethane and cooled to 0° C. in an ice bath. It was then treated with 3-chloroperoxybenzoic acid (0.6857 mmol) and continued to stir at 0° C. for 1 hr. Reaction mixture was then quenched with 10% aq solution of sodium thiosulfate. It was then diluted with dichloromethane and washed with sodium bicarbonate. Organic portions were collected and washed with brine, then dried over anhydrous sodium sulfate, filtered and concentrated to afford 5117E in quantitative yield.



5117E

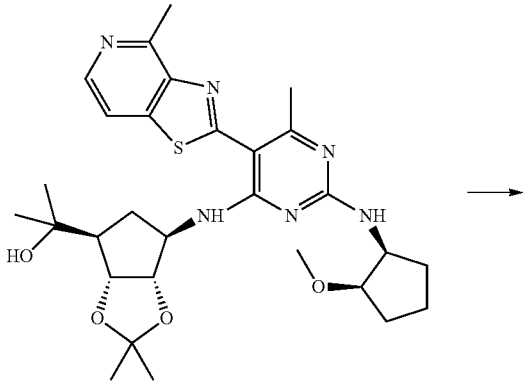
-continued



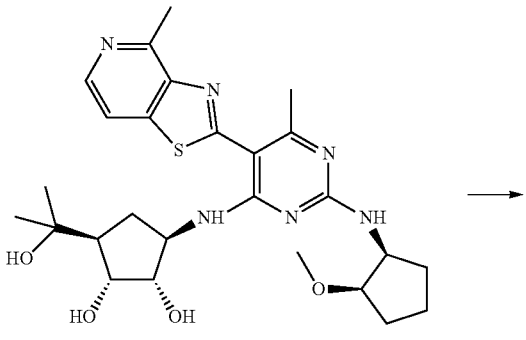
5117

In a 5 mL Biotage microwave vial 5117E (0.1199 mmol) was dissolved in acetonitrile followed by addition of 2,6-difluorobenzylamine (0.1439 mmol). Reaction mixture was stirred at 80° C. in oil bath for 24 hrs. Then it was concentrated and purified by silica gel column to afford 5117 as a yellow solid in 64% yield.

Preparation of 5144 and 5145:

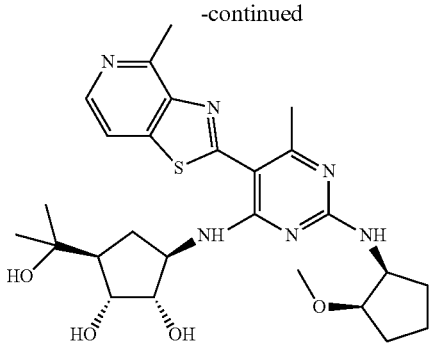


5144A

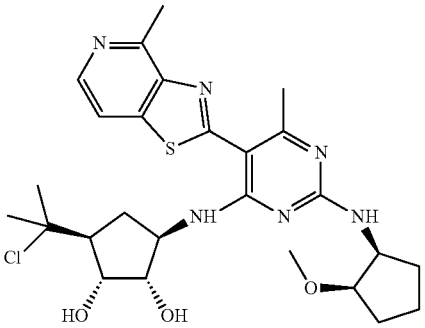


5144 (crude)

-continued



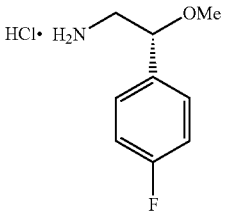
5144



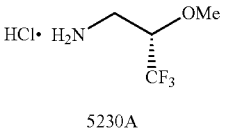
5145

Compound 5144A (prepared using procedures described earlier) was converted to crude 5144HCl salt using Procedure F, step 3. After drying analysis showed some by-product formation. Purification on a C18 reverse phase column eluting with 10-90% Acetonitrile/Water gave pure 5144 and a pure by-product 5145.

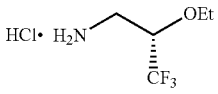
Preparation of Amine Intermediates Required for Examples 5226-5235:



5226A

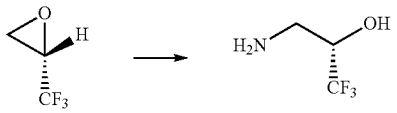


5230A



5233A

Step 1.

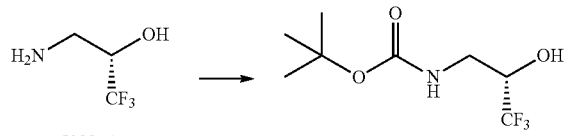


5233Aa

5233Ab

A reaction tube was charged with a solution of (S)-2-(trifluoromethyl)oxirane, 5233Aa (1.12 g, 10.0 mmol) in THF (50 mL) and water (10 mL). Sodium azide (2.0 eq, 1.30 g) and ammonium chloride (2.0 eq, 1.07 g) were added and the tube was sealed. The reaction mixture was heated (oil bath at 65° C.) for 3 h. The mixture was treated with aqueous 2 N NaOH (20 mL) and the product was taken into ether (150 mL). Upon separation, the organic layer was washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated to almost dryness in rotavap (no heating in water bath). The residue was dissolved in methanol (50 mL) and treated with a catalytic amount of 10% palladium on carbon (tip of spatula). The mixture was hydrogenated at room temperature (balloon pressure) for 2 h. The mixture was diluted with methanol (100 mL) and the solids were removed by filtration. The filtrate was concentrated in rotavap to give the crude product 5233Ab (700 g, 54%) as a white powder.

Step 2.

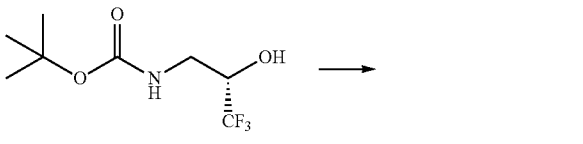


5233Ab

5233Ac

The amino-alcohol 5233Ab (700 mg, 5.42 mmol) was dissolved in THF (10 mL) and treated with a solution of Boc anhydride (1.0 eq, 1.18 g) in THF (15 mL) and Hunig's base (1.0 eq, 0.943 mL, d 0.742). The reaction mixture was stirred for 3 h. TLC (20% ethyl acetate in hexanes) showed a new spot. The mixture was diluted with ethyl acetate (80 mL) and washed with aqueous 1 M HCl (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a Redisep® gold cap (40 g) silica gel column (gradient: 0 to 40% ethyl acetate in hexanes) to give the product 5233Ac (1.25 g, 100%) as a colorless oil.

Step 3.

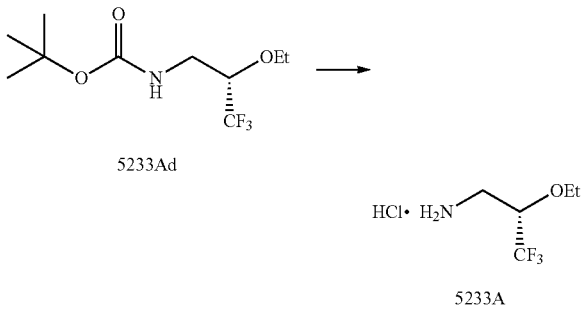


5233Ac

5233Ad

The N-Boc-protected amino-alcohol 5233Ac (620 mg, 2.705 mmol) was suspended in toluene (5 mL) and enough THF was added to obtain a homogeneous solution (aprox 1 mL). The resulting solution was treated with iodoethane (3.0 eq, 0.650 mL, d 1.950). The mixture was placed in an ice-water bath and treated with aqueous 50% NaOH (2.7 mL) and tetrabutylammonium hydrogen sulfate (0.2 eq, 183 mg). The cooling bath was removed the slurry was stirred for 24 h at 45° C. TLC (20% ethyl acetate in hexanes) showed about 80% conversion. The mixture was diluted with ethyl acetate (25 mL) and water (5 mL) and layers were separated. The aq layer was back-extracted with ethyl acetate (2×25 mL) and the combined organic layers were washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a Redisep® (40 g) silica gel column (gradient: 0 to 25% ethyl acetate in hexanes) to give the product 5233Ad (365 mg, 53%) as a white powder. Unreacted starting material was also recovered (247 mg, 40%).

Step 4.



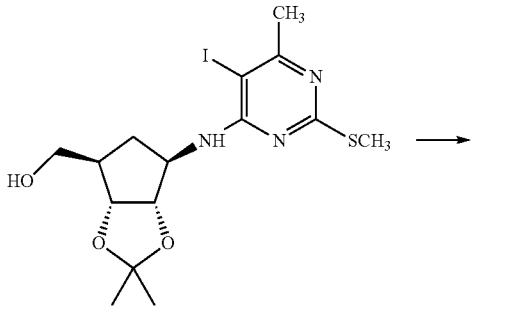
5233Ad

5233A

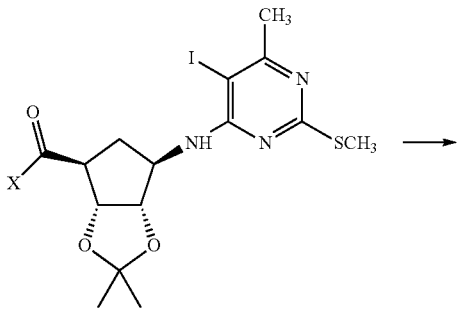
The N-Boc protected amine 5233Ad (345 mgm 1.341 mmol) was dissolved in 4 M HCl in dioxane. The mixture was stirred for 1 h and TLC showed a complete reaction. The mixture was concentrated to dryness in rotavap to give the crude product 5233A (ca 100%, 258 mg) as a white powder. No further purification was carried out.

The amine intermediates 5226A and 5230A were prepared using a similar procedure.

Preparation of 5295:



5295aa



5295a: X = OMe

5295b: X = NH_2

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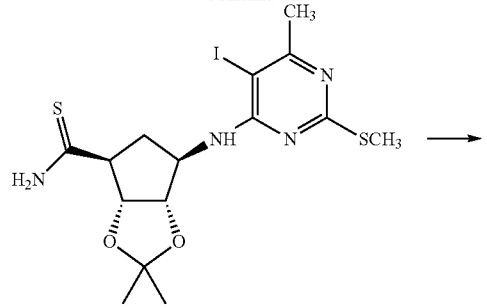
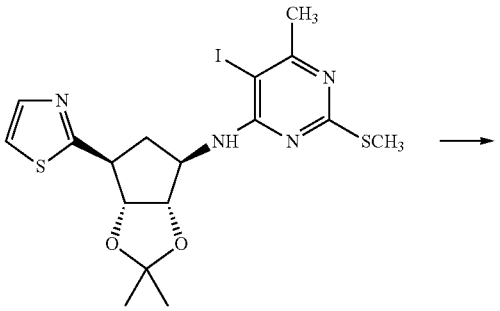
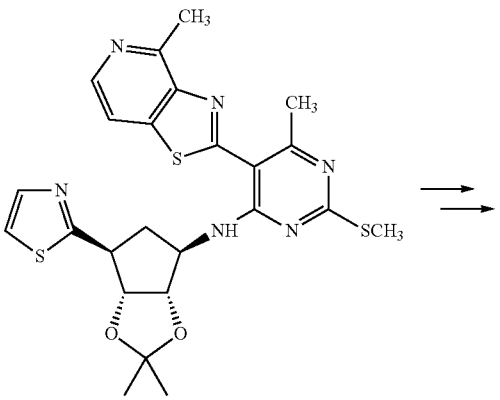


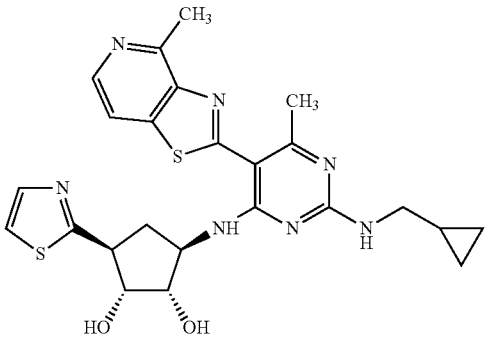
5295c



5295d



5295e



5295

Step A:

A solution of 5295aa (8.00 g, 17.7 mmoles), copper (I) oxide (5.06 g, 35.3 mmol), copper (I) iodide (6.76 g, 35.5 mmol), (diacetoxyiodo)benzene (30.3 g, 94.0 mmol), and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) (8.30 g, 53.1 mmol) in methylene chloride (200 mL) was stirred at room temperature for 18 h. The resulting solution was vacuum-filtered through diatomaceous earth, the filter pad was rinsed with methylene chloride, and the combined filtrates were concentrated under reduced pressure. The residue was redissolved in 1:1 toluene/methanol (200 mL) and trimethylsilyldiazomethane (1.0 M in diethyl ether, 320 mL, 320 mmol) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure to afford a brown slurry which was purified by chromatography [silica, 5-20% (10% methanol in ethyl acetate)/heptane] to afford 5295a (3.41 g, 40%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (d, J=6.3 Hz, 1H), 4.91 (d, J=5.7 Hz, 1H), 4.57 (d, J=5.7 Hz, 1H), 4.54 (app t, J=6.1 Hz, 1H), 3.78 (s, 3H), 3.12 (d, J=8.3 Hz, 1H), 2.54 (s, 3H), 2.52 (s, 3H), 2.16 (m, 1H), 1.48 (s, 3H), 1.28 (s, 3H); ESI MS m/z 480 $[M+H]^+$.

Step B:

A solution of 5295a (1.0 g, 2.08 mmol) in ammonia (7 N in methanol, 100 mL) was stirred in a sealed tube at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure to afford 5295b (0.94 g, quantitative) as a yellow waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J=7.2 Hz, 1H), 5.82 (br s, 1H), 5.62 (br s, 1H), 4.80 (d, J=5.4 Hz, 1H), 4.70 (t, J=7.1 Hz, 1H), 4.62 (d, J=5.4 Hz, 1H), 3.77 (d, 5.6 Hz, 1H), 3.73-3.68 (m, 1H), 2.92 (d, J=8.7 Hz, 1H), 2.53 (s, 3H), 2.52 (s, 3H), 2.10-2.05 (m, 1H), 1.48 (s, 3H), 1.28 (s, 3H); ESI MS m/z 465 $[M+H]^+$.

Step C:

A solution of 5295b (0.200 g, 0.440 mmoles) and 2,4-bis (4-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-disulfide (Lawesson's Reagent) (0.134 g, 0.333 mmol) in anhydrous tetrahydrofuran (3.0 mL) was heated at 60° C. for 12 h. The reaction was cooled, diluted with ethyl acetate (30 mL), and washed sequentially with saturated sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography [silica, 5-20% (10% methanol in ethyl acetate)/heptane] to afford 5295c (0.077 g, 36%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.38 (br s, 1H), 7.20-7.10 (br s, 1H), 6.50-6.38 (br s, 1H), 4.88-4.85 (m, 1H), 4.68-4.58 (m, 2H), 3.21-3.14 (m, 1H), 2.77-2.67 (m, 1H), 2.52 (s, 3H), 2.51 (s, 3H), 2.36-2.27 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ESI MS m/z 481 $[M+H]^+$.

Step D:

Chloroacetaldehyde (50% in water, 0.106 mL, 0.836 mmol) was added dropwise at room temperature to a solution of 5295c (0.100 g, 0.209 mmoles) and potassium bicarbonate (0.083 g, 0.835 mmol) in dimethoxyethane (0.5 mL) and the reaction mixture was stirred at room temperature overnight. Analysis by LC/MS showed the conversion of starting material to the intermediate dihydrothiazol-4-ol (m/z 522 $[M+H]^+$). The reaction mixture was vacuum-filtered through diatomaceous earth and the filtrate was concentrated. The residue was redissolved in dimethoxyethane (1.0 mL) and treated with a solution of trifluoroacetic anhydride (0.087 mL, 0.626 mmoles) and pyridine (0.050 mL, 0.626 mmoles) in dimethoxyethane (0.2 mL). The reaction mixture was stirred for 10 min and concentrated under reduced pressure. The residue was purified by chromatography [silica, 5% ethyl acetate/(methylene chloride/hexanes 1:1)] to afford 5295d (0.073 g, 69%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.77 (d, J=3.3 Hz, 1H), 7.28 (d, J=3.3 Hz, 1H), 4.80 (d, J=5.5 Hz, 1H), 4.75 (t, J=7.2 Hz, 1H), 4.59 (d, J=5.5 Hz, 1H), 3.85 (d,

J=8.2 Hz, 1H), 2.87-2.87 (m, 1H), 2.53 (s, 3H), 2.49 (s, 3H), 2.31 (m, 1H), 1.53 (s, 3H), 1.29 (s, 3H); ESI MS m/z 505 $[M+H]^+$.

Step E:

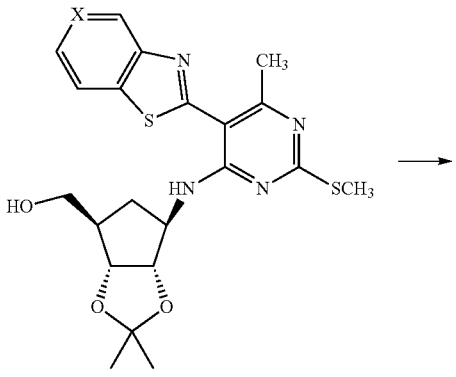
A microwave tube was charged with a solution of 4-methylthiazolo[4,5-c]pyridine (0.046 g, 0.306 mmol), thiazole 5295d (0.100 g, 0.204 mmoles), copper (I) iodide (0.020 g, 0.102 mmoles), and cesium(II)carbonate (0.332 g, 1.02 mmole) in N,N-dimethylformamide (2.0 mL) and the reaction mixture was gently sparged with argon for 5 min Tetrakis(triphenylphospine)palladium(0) (0.047 g, 0.041 mmoles) was added and the argon sparge was continued for an additional 2 min. The microwave vessel was sealed and irradiated in a microwave reactor (CEM microwave reactor) at 100° C. for 0.5 h. The reaction was cooled, diluted with tetrahydrofuran, and vacuum-filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (silica, 5-80% tetrahydrofuran/hexanes) to afford 5295e (0.042 g, 26%) as a solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 7.68-7.56 (m, 1H), 7.52-7.49 (m, 1H), 6.83 (d, J=3.2 Hz, 1H), 6.42 (d, J=3.2 Hz, 1H), 4.90 (d, J=5.8 Hz, 1H), 4.20-4.17 (m, 1H), 2.94 (s, 3H), 2.85-2.79 (m, 1H), 2.56 (s, 3H), 2.51 (s, 3H), 2.31-2.15 (m, 1H), 1.54 (s, 3H), 1.30 (s, 3H); ESI MS m/z 527 $[M+H]^+$.

(Note 1: CEM Microwave Reactor)

Step F:

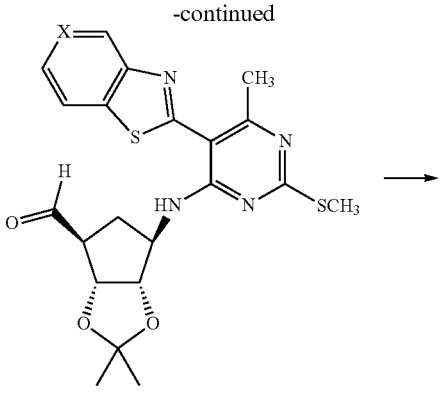
The title compound 5295 was prepared according to procedures described earlier: using compound 5295e (0.042 g, 0.080 mmoles) and cyclopropylmethylamine (0.100 mL) resulted in 5295 (0.009 g, 19%) as a fine yellow powder: ^{1}H NMR (500 MHz, CD_3OD) δ 8.62 (m, 2H), 7.58 (m, 1H), 7.48 (m, 1H), 4.72 (m, 1H), 4.17 (m, 2H), 3.65 (m, 1H), 3.49 (m, 2H), 3.20 (s, 3H), 2.87 (m, 1H), 2.62 (s, 3H), 1.98 (m, 1H), 2.22 (m, 1H), 0.59 (m, 2H), 0.38 (m, 2H); HPLC (Method A) 95.6% (AUC), t_R=10.17 min; ESI MS m/z 510 $[M+H]^+$.

Preparation of 5290:

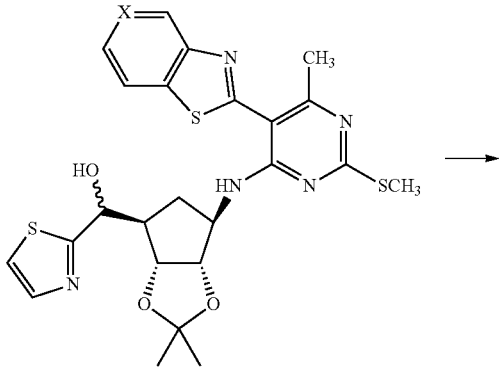


X = CH: 5290aa
X = N: 5290a

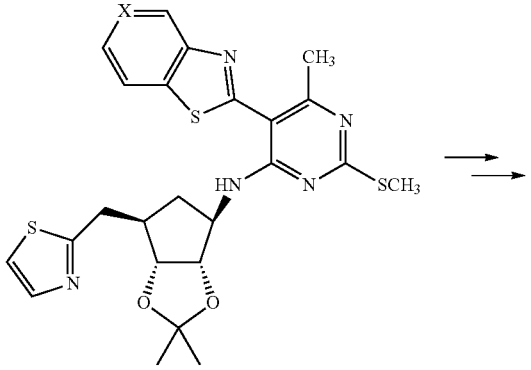
-continued



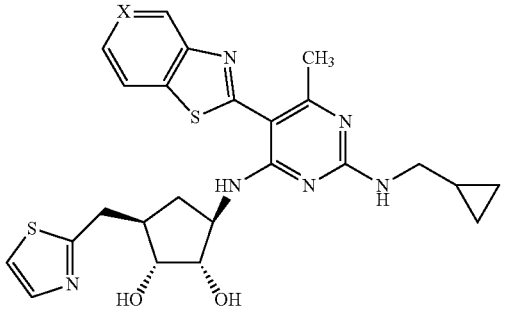
X = CH: 5290bb
X = N: 5290b



X = CH: 5290cc
X = N: 5290c



X = CH: 5290dd
X = N: 5290d



5290

Step A:

Dess-Martin periodinane (0.815 g, 1.92 mmol) was added to a solution of 5290aa (X=CH, 0.735 g, 1.69 mmol) in

methylene chloride (25 mL) at 0° C. and the reaction mixture was gradually warmed to approximately 15° C. over 2 h. The reaction mixture was quenched with 10% sodium sulfite solution (70 mL) and saturated sodium bicarbonate solution (70 mL) then extracted with ethyl acetate (2×100 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica, 0-10% methanol/ethyl acetate) to afford 5290bb (0.767 g, quantitative) as an off-white solid: ESI MS m/z 457 $[M+H]^+$.

The intermediate 5290b (X=N) was prepared according to the method described for 5290bb: oxidation of 5290a (1.00 g, 2.18 mmol) afforded 5290b (0.787 g, 79%) as a light yellow solid: ESI MS m/z 458 $[M+H]^+$.

Step B:

A solution of n-butyllithium (1.6 M in hexanes, 13.5 mL, 21.9 mmol) was added at −78° C. to a solution of thiazole (1.80 g, 85.1 mmol) in anhydrous tetrahydrofuran (10 mL) and the reaction mixture was stirred at −78° C. for 15 min. After this time, a solution of compound 5290bb (X=CH, 2.10 g, 4.38 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise via addition funnel, and the reaction mixture was warmed to 0° C. over 2 h. The reaction mixture was then quenched with saturated ammonium chloride solution (50 mL) and partitioned between water and ethyl acetate (100 mL). The phases were separated and the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica, 0-10% methanol/ethyl acetate) to afford 5290 cc (1.30 g, 54%) as an off-white solid: ESI MS m/z 542 $[M+H]^+$.

The intermediate 5290c was prepared according to the method described for 5290 cc: compound 5290b (0.880 g, 1.92 mmol) afforded 5290c (0.380 g, 37%) as a light yellow solid: ESI MS m/z 615 $[M+H]^+$.

Step C:

Methanesulfonyl chloride (0.025 mL, 0.323 mmol) was added dropwise at 0° C. to a solution of compound 5290 cc (0.117 g, 0.215 mmol) and triethylamine (0.089 mL, 0.645 mmol) in toluene (1.0 mL). The reaction mixture was warmed gradually to room temperature over 2 h. After this time, the reaction mixture was diluted with ethyl acetate (1.0 mL) and treated with palladium on carbon (10% wt, 0.150 g). The reaction mixture was purged with nitrogen gas followed by hydrogen gas. The reaction mixture was stiffed under a hydrogen atmosphere (balloon) at room temperature 18 h. After this time, the reaction mixture was diluted with methanol (20 mL), vacuum-filtered through diatomaceous earth, and concentrated under reduced pressure. The resulting residue was purified by chromatography (silica, 0-20% ethyl acetate/hexanes) to afford 5290dd (0.043 g, 38%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, J=5.6 Hz, 1H), 7.98 (d, J=7.9 Hz, 1H), 7.90 (d, J=7.9 Hz, 1H), 7.52 (d, J=3.3 Hz, 1H), 7.49 (dt, J=7.9, 1.2 Hz, 1H), 7.39 (dt, J=7.9, 1.2 Hz, 1H), 7.15 (d, J=3.3 Hz, 1H), 4.71 (dd, J=6.2, 2.2 Hz, 1H), 4.59-4.52 (m, 2H), 3.39 (dd, J=14.7, 7.6 Hz, 1H), 3.15 (dd, J=14.7, 8.0 Hz, 1H), 2.72 (s, 3H), 2.68-2.64 (m, 1H), 2.60 (s, 3H), 2.60-2.48 (m, 1H), 1.72 (dt, J=13.3, 5.4 Hz, 1H), 1.50 (s, 3H), 1.29 (s, 3H); ESI MS m/z 526 $[M+H]^+$.

The intermediate 5290d was prepared according to the method described for 5290dd: compound 5290c (0.400 g, 0.368 mmol) afforded 5290d (0.058 g, 26%) as a light yellow solid: ESI MS m/z 527 $[M+H]^+$.

The title compound 5290 was prepared according to procedures described earlier: compound 5290d (0.008 g, 0.015 mmol) and cyclopropylmethanamine (1.0 mL) afforded 5290 (0.006 g, 81%) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD+$CDCl_3$+DMSO-d_6) δ 9.18 (s, 1H), 8.42 (d, J=5.45 Hz, 1H), 8.10 (d, J=5.45 Hz, 1H), 7.67 (d, J=3.35 Hz, 1H), 7.41 (d, J=3.35 Hz, 1H), 4.42-4.33 (m, 1H), 4.05-3.97 (m, 1H), 3.90 (t, J=5.85 Hz, 1H), 3.39 (dd, J=14.8, 5.7 Hz, 1H), 3.28-3.24 (m, 5H), 3.11 (dd, J=14.8, 8.7 Hz, 1H), 2.66 (s, 3H), 2.56-2.48 (m, 2H), 1.13-1.08 (m, 2H), 0.90-0.85 (m, 1H), 0.52-0.49 (m, 2H), 0.284-0.225 (m, 2H); HPLC (Method A) 97.7% (AUC), t_R=8.11 min; ESI MS m/z 510 $[M+H]^+$.

ASSAYS

Cell-Based HCV Replicon Assay

To measure cell-based anti-HCV activity of the compounds of the present invention, replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated Nunc plates in the presence of the compound of the invention. Various concentrations of a compound of the invention, typically in 10 serial 2-fold dilutions, were added to the assay mixture, the starting concentration of the compound ranging from 25 μM to 1 μM. The final concentration of DMSO was 0.5%, fetal bovine serum was 10%, in the assay media. Cells were harvested on day 3 by the addition of 1× cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in 5B. The PCR primers were: 5B.2F, ATGGACAGGCGCCCTGA; 5B.2R, TTGATGGGCAGCTTGGTTTC; the probe sequence was FAM-labeled CACGCCATGCGCTGCGG. GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacturer (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM® 7900HT Sequence Detection System using the following program: 48'C for 30 min, 95'C for 10 min, 40 cycles of 95'C for 15 sec, 60'C for 1 min. The ΔCT values (CT_{5B}-CT_{GAPDH}) were plotted against the concentration of test compound and fitted to the sigmoid dose-response model using Graph Pad PRISM® software. EC_{50} was defined as the concentration of inhibitor necessary to achieve ΔCT=1 over the projected baseline; EC_{90} the concentration necessary to achieve ΔCT=3.2 over the baseline. Alternatively, to quantitate the absolute amount of replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from PE Applied Biosystems. Such an assay procedure was described in detail in e.g. Malcolm et al., *Antimicrobial Agents and Chemotherapy* 50: 1013-1020 (2006).

HCV Replicon assay data for compounds of the invention that were tested were obtained using the above method.

In other embodiments, the compounds of the invention have a structural formula as depicted in Tables IIA, IIB, IIC, and IID below and include tautomers, and pharmaceutically acceptable salts, esters, prodrugs, isomers, and solvates of such compounds and such tautomers. The compounds shown in these tables were made according to the methods described herein or analogous thereto.

HCV Replicon assay data for compounds of the invention shown in Table IIA that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIA as a falling within the following range: "A"—less than or equal to about 0.5 μM.

TABLE IIA

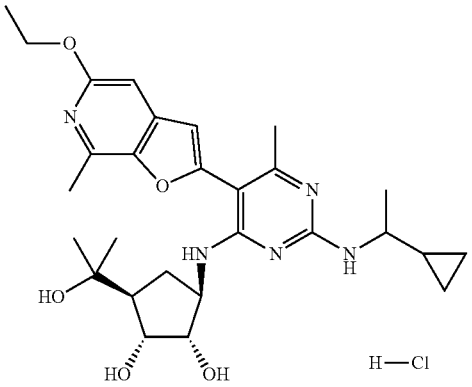
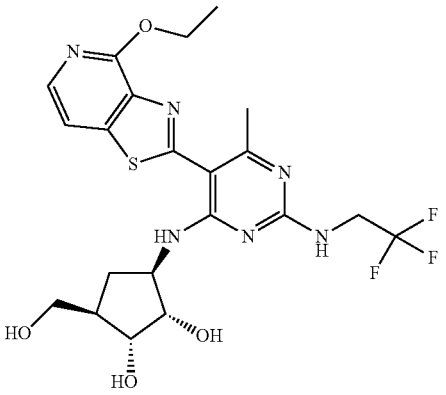
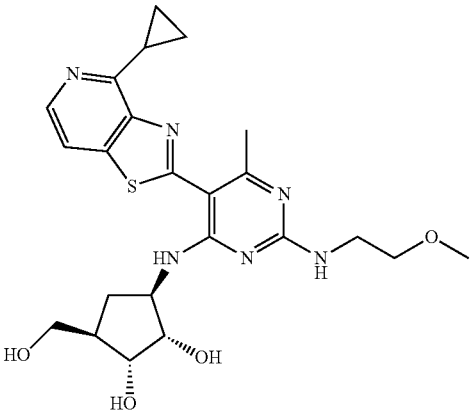
Compd #	Structure	1H NMR data	MS (M + H)+
2415		(DMSO-d6) δ 0.24-0.42 (m, 2H), 0.41-0.57 (m, 2H), 1.02 (s, 3H), 1.03-1.12 (m, 1H), 1.12 (s, 3H), 1.25-1.38 (m, 1H), 1.29-1.38 (m, 1H), 1.31 (app q, 6H, J = 7.0 Hz), 1.69-1.78 (m, 1H), 1.88-1.97 (m, 1H), 2.24 (s, 3H), 2.57 (s, 3H), 3.50-3.80 (m, 3H), 4.30 (app q, 2H, J = 7.0 Hz), 4.26-4.34 (m, 1H), 6.86 (s, 1H), 7.02 (s, 1H), 7.86 (br s, 1H), 7.95 (br s, 1H), 12.62 (br s, 1H).	526.3
2502		(DMSO-d6) δ 1.05-1.22 (m, 1H), 1.45 (t, 3H, J = 7.0 Hz), 1.93-2.05 (m, 1H), 2.27-2.41 (m, 1H), 2.55 (s, 3H), 3.30-3.40 (m, 1H), 3.42-3.51 (m, 1H), 3.69-3.76 (m, 1H), 3.73-3.82 (br s, 1H), 4.03-4.40 (m, 3H), 4.44-4.60 (m, 1H), 4.52 (q, 2H, J = 7.1 Hz), 7.71 (d, 1H, J = 5.5 Hz), 7.75-7.83 (m, 1H), 8.04 (d, 1H, J = 5.6 Hz), 9.60-9.90 (m, 1H).	515.2
2504		(DMSO-d6) δ 1.11-1.22 (m, 1H), 1.23-1.32 (m, 2H), 1.36-1.44 (m, 2H), 1.88-2.00 (m, 1H), 2.17-2.28 (m, 1H), 2.45 (s, 3H), 2.98-3.06 (m, 1H), 3.32 (s, 3H), 3.30-3.40 (m, 2H), 3.52-3.59 (m, 2H), 3.60-3.70 (m, 3H), 3.73-3.81 (m, 1H), 4.40 (app quint, 1H, J = 7.7 Hz), 7.96 (br s, 1H, 8.20 (d, 1H, J = 5.1 Hz), 8.45 (d, 1H, J = 5.7 Hz), 9.08 (br s, 1H).	487.2

TABLE IIA-continued

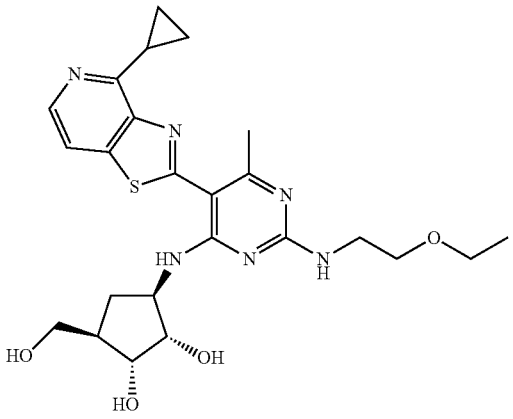
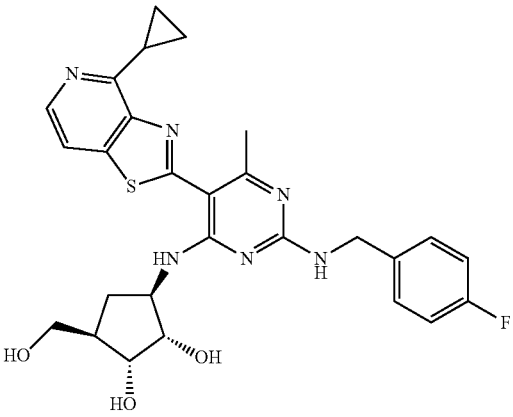
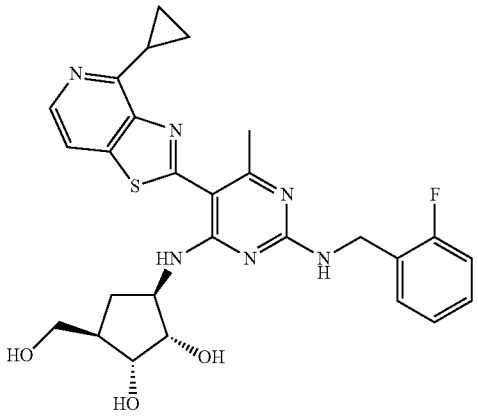
Compd #	Structure	1H NMR data	MS (M + H)+
2505		(DMSO-d6) δ 1.15 (t, 3H, J = 7.0 Hz), 1.12-1.21 (m, 1H), 1.22-1.29 (m, 2H), 1.36-1.44 (m, 2H), 1.88-2.00 (m, 1H), 2.17-2.28 (m, 1H), 2.45 (s, 3H), 2.98-3.06 (m, 1H), 3.30-3.40 (m, 2H), 3.51 (q, 2H, J = 7.0 Hz), 3.56-3.66 (m, 3H), 3.65-3.69 (m, 2H), 4.40 (app quint, 1H, J = 7.7 Hz), 7.91 (br s, 1H), 8.12-8.18 (m, 1H), 8.45 (d, 1H, J = 5.6 Hz), 9.12 (br s, 1H).	501.2
2508		(DMSO-d6) δ 1.02-1.11 (m, 1H), 1.22-1.29 (m, 2H), 1.38-1.46 (m, 2H), 1.88-1.98 (m, 1H), 1.97-2.09 (m, 1H), 2.45 (s, 3H), 2.96-3.04 (m, 1H), 3.32 (d, 2H, J = 5.2 Hz), 3.67 (app t, 1H, J = 4.7 Hz), 3.73 (dd, 1H, J = 5.5, 7.0 Hz), 4.42 (app quint, 1H, J = 7.8 Hz), 4.61-4.67 (m, 2H), 7.16-7.23 (m, 2H), 7.45-7.51 (m, 2H), 8.12-8.17 (m, 1H), 8.44 (d, 1H, J = 5.7 Hz), 8.48 (br s, 1H), 9.00 (br s, 1H).	537.2
2509		(DMSO-d6) δ 0.98-1.08 (m, 1H), 1.13-1.22 (m, 2H), 1.18-1.27 (m, 2H), 1.85-1.96 (m, 1H), 1.94-2.05 (m, 1H), 2.43 (s, 3H), 2.94-3.03 (m, 1H), 3.66 (app t, 1H, J = 5.0 Hz), 3.70-3.76 (m, 1H), 4.39 (app quint, 1H, J = 7.9 Hz), 4.71 (dq, 2H, J = 6.1, 15.5 Hz), 7.18-7.25 (m, 2H), 7.32-7.40 (m, 1H), 7.50 (app t, 1H, J = 7.5 Hz), 8.05 (d, 1H, J = 5.5 Hz), 8.36 (br s, 1H), 8.41 (d, 1H, J = 5.4 Hz), 9.11 (br s, 1H).	537.2

TABLE IIA-continued

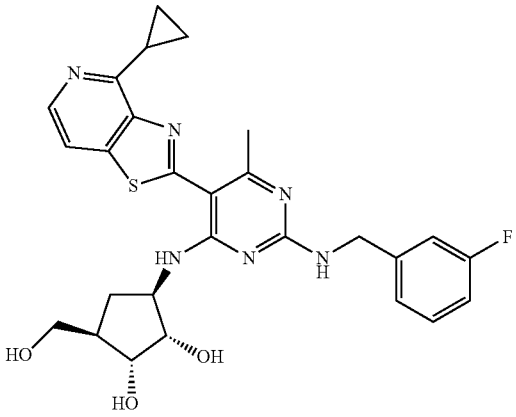
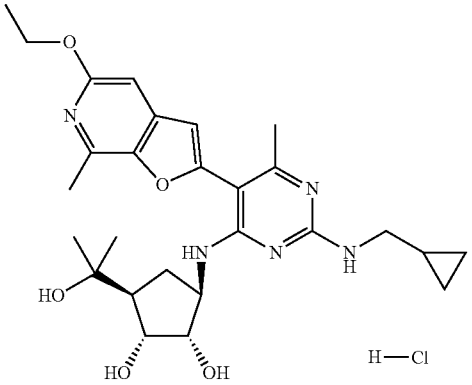
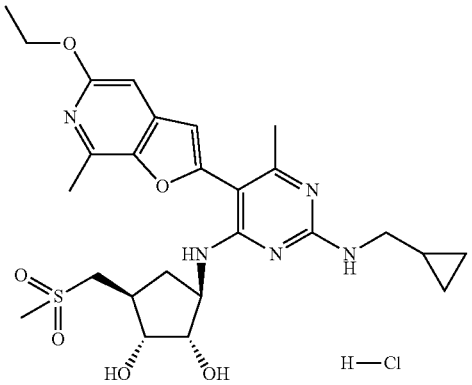
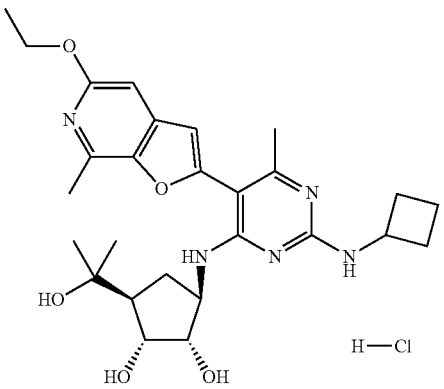
Compd #	Structure	1H NMR data	MS (M + H)+
2510		(DMSO-d6) δ 1.00-1.10 (m, 1H), 1.20-1.28 (m, 2H), 1.30-1.39 (m, 2H), 1.85-2.01 (m, 2H), 2.44 (s, 3H), 2.95-3.04 (m, 1H), 3.31 (d, 2H, J = 5.0 Hz), 3.73 (dd, 1H, J = 5.0, 7.4 Hz), 4.38 (app quint, 1H, J = 7.7 Hz), 4.62-4.76 (m, 2H), 7.11 (dt, 1H, J = = 2.4, 9.0 Hz), 7.22-7.29 (dd, 2H, J = 7.6, 12.1 Hz), 7.38-7.45 (m, 1H), 8.12-8.18 (m, 1H), 8.43 (d, 1H, J = 5.7 Hz), 8.50 (br s, 1H), 9.02 (br s, 1H).	537.2
2511		(DMSO-d6) δ 0.28-0.35 (m, 2H), 0.47-0.55 (m, 2H), 1.02 (s, 3H), 1.12 (s, 3H), 1.08-1.17 (m, 1H), 1.29-1.38 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz), 1.69-1.78 (m, 1H), 1.90-2.00 (m, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 3.29-3.35 (m, 1H), 3.75-3.81 (m, 1H), 4.30 (q, 2H, J = 7.0 Hz), 4.34-4.42 (m, 1H), 6.83 (s, 1H), 7.03 (s, 1H), 7.86 (br s, 1H), 12.77 (br s, 1H).	512.3
2512		(DMSO-d6) δ 0.28-0.37 (m, 2H), 0.47-0.55 (m, 2H), 1.09-1.41 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz), 2.26 (s, 3H), 2.30-2.50 (m, 2H), 2.57 (s, 3H), 2.98 (s, 3H), 2.95-3.08 (m, 1H), 3.28-3.40 (m, 3H), 3.56-3.62 (m, 1H), 3.81-3.84 (m, 1H), 4.30 (q, 2H, J = 7.0 Hz), 4.32-4.45 (m, 1H), 7.89-8.02 (m, 2H), 12.91 (br s, 1H).	546.2
2513		(DMSO-d6) δ 1.02 (s, 3H), 1.12 (s, 3H), 1.28-1.38 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz), 1.68-1.83 (m, 4H), 1.90-2.03 (m, 1H), 2.02-2.20 (m, 4H), 2.25 (s, 3H), 2.28-2.40 (m, 3H), 3.66-3.75 (m, 1H), 4.30 (q, 2H, J = 7.0 Hz), 4.32-4.42 (m, 1H), 6.87 (s, 1H), 7.03 (s, 1H), 7.86 (br s, 1H), 8.21 (br s, 1H), 12.80 (br s, 1H).	512.3

TABLE IIA-continued

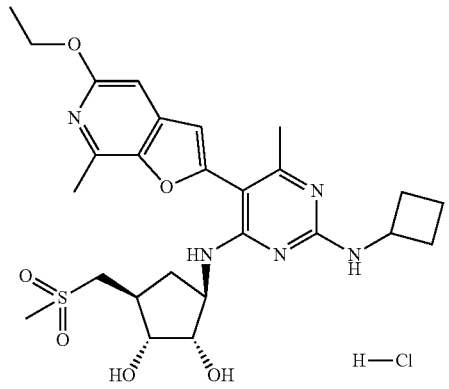
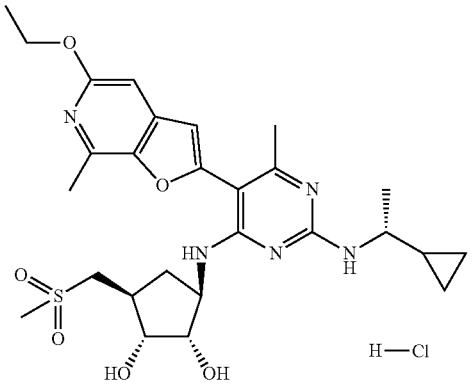
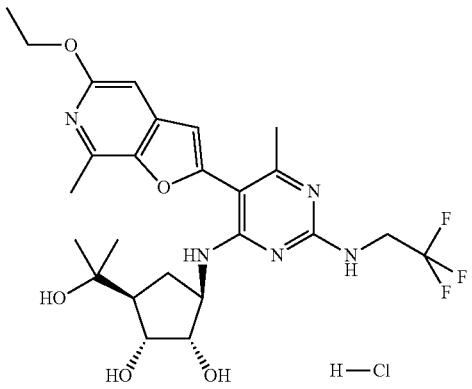
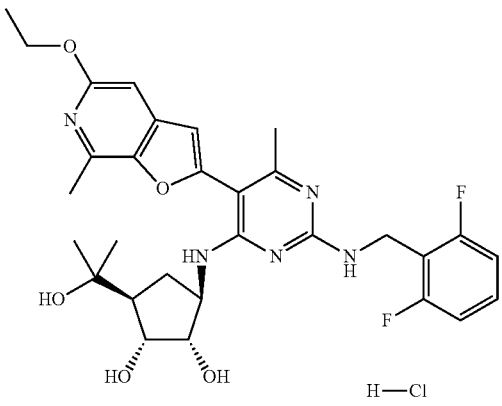
Compd #	Structure	1H NMR data	MS (M + H)+
2514		(DMSO-d6) δ 1.20-1.30 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz), 1.69-1.81 (m, 2H), 2.00-2.11 (m, 1H), 2.23 (br s, 3H), 2.30-2.45 (m, 4H), 2.57 (s, 3H), 2.98 (s, 3H), 3.04 (dd, 1H, J = 10.1, 14.0 Hz), 3.35 (dd, 1H, J = 3.7, 13.9 Hz), 3.57-3.62 (m, 1H), 3.81-3.88 (m, 1H), 4.30 (q, 2H, J = 7.0, 13.9 Hz), 4.34-4.45 (m, 2H), 6.88 (s, 1H), 7.05 (s, 1H), 8.00 (br s, 1H), 8.26 (br s, 1H), 12.96 (br s, 1H).	546.2
2516		(DMSO-d6) δ 0.25-0.41 (m, 2H), 0.42-0.57 (m, 2H), 1.04-1.12 (m, 1H), 1.29-1.38 (m, 1H), 1.31 (app q, 6H, J = 7.0 Hz), 2.25 (s, 3H), 2.25-2.42 (m, 2H), 2.56 (s, 3H), 2.98 (s, 3H), 3.02 (dd, 1H, J = 4.0, 10.1 Hz), 3.35 (dd, 1H, J = 3.8, 14.0 Hz), 3.52-3.74 (m, 2H), 3.82 (app t, 1H, J = 5.2 Hz), 4.30 (q, 2H, J = 7.0 Hz), 4.26-4.37 (m, 1H), 6.87 (s, 1H), 7.04 (s, 1H), 7.87-8.01 (m, 2H), 12.70 (br s, 1H).	560.3
2518		(DMSO-d6) δ 1.02 (s, 3H), 1.12 (s, 3H), 1.23-1.38 (m, 1H), 1.33 (t, 3H, J = 7.0 Hz), 1.68-1.80 (m, 1H), 1.90-2.02 (m, 1H), 2.28 (s, 3H), 2.58 (s, 3H), 3.50-3.82 (m, 2H), 4.30 (app q, 2H, J = 7.0 Hz), 4.25-4.50 (m, 1H), 6.88 (s, 1H), 7.06 (s, 1H), 8.13 (br s, 1H), 8.33 (br s, 1H).	540.2
2519		(DMSO-d6) δ 1.02 (s, 3H), 1.14 (s, 3H), 1.22-1.38 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz), 1.74-1.87 (m, 2H), 2.23 (s, 3H), 2.56 (s, 3H), 3.50-3.82 (m, 2H), 4.29 (app q, 2H, J = 7.0 Hz), 4.35-4.50 (m, 1H), 4.60-4.70 (m, 1H), 4.76-4.86 (m, 1H), 6.86 (s, 1H), 7.01 (s, 1H), 7.08-7.26 (m, 1H), 7.38-7.61 (m, 1H), 8.03-8.10 (m, 1H), 8.32 (br s, 1H).	584.3

TABLE IIA-continued

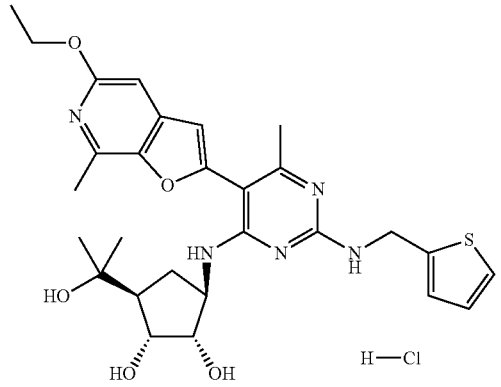
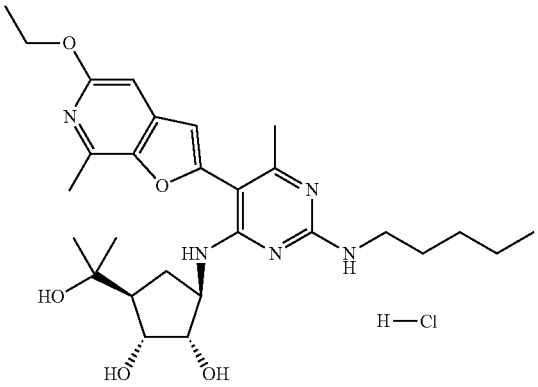
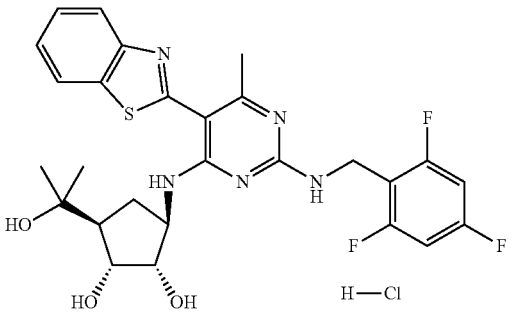
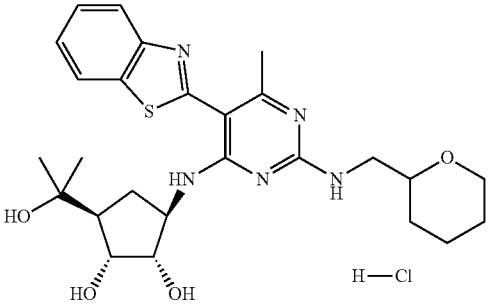
Compd #	Structure	1H NMR data	MS (M + H)+
2520		(DMSO-d6) δ 1.00 (s, 3H), 1.12 (s, 3H), 1.21-1.34 (m, 1H), 1.33 (t, 3H, J = 7.0 Hz), 1.68-1.78 (m, 1H), 1.82-1.93 (m, 1H), 2.25 (s, 3H), 2.57 (s, 3H), 3.50-4.00 (m, 2H), 4.30 (app q, 2H, J = 7.0 Hz), 4.42-4.56 (m, 1H), 4.70-4.78 (m, 1H), 4.82-4.90 (m, 1H), 6.88 (s, 1H), 6.99 (dd, 1H, J = 3.5, 5.1 Hz), 7.04 (s, 1H), 7.14 (br d, 1H, J = 3.2 Hz), 7.45 (dd, 1H, J = 1.0, 5.0 Hz), 8.07 (br d, 1H, J = 7.6 Hz), 8.38 (br s, 1H), 13.15 (br s, 1H).	554.2
2521		(DMSO-d6) δ 0.87-0.92 (m, 1H), 1.01 (s, 3H), 1.12 (s, 3H), 1.23-1.38 (m, 9H), 1.55-1.64 (m, 2H), 1.78-1.76 (m, 1H), 1.90-2.05 (m, 2H), 2.25 (s, 3H), 2.58 (s, 3H), 3.05-3.42 (m, 1H), 3.42-3.52 (m, 1H), 3.50-3.76 (m, 1H), 3.76-3.82 (m, 1H), 4.31 (q, 2H, J = 7.0 Hz), 4.32 (m, 1H), 6.89 (s, 1H), 7.04 (s, 1H), 7.91 (br s, 1H), 8.00 (br d, J = 7.1 Hz), 12.97 (br s, 1H).	528.3
2526		(DMSO-d6) δ 1.05 (s, 3H), 1.16 (s, 3H), 1.10-1.26 (m, 1H), 1.82 (br s, 1H), 2.08-2.17 (m, 1H), 2.54 (s, 3H), 3.61 (br s, 1H), 3.85 (br s, 1H), 4.22-4.33 (m, 2H), 4.47- (dd, 1H, J = 5.0, 13.9 Hz), 4.56 (br s, 1H), 4.64 (br s, 1Hz), 7.12 (t, 1H, J = 8.5 Hz), 7.38-7.43 (m, 1H), 7.49-7.54 (m, 1H), 7.59 (br s, 1H), 7.97 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 7.7 Hz), 9.66 (br s, 1H).	560.2
2527		(DMSO-d6) δ 1.04 (s, 3H), 1.15 (s, 3H), 1.18-1.36 (m, 3H), 1.41-1.53 (m, 3H), 1.58-1.67 (m, 1H), 1.72-1.85 (m, 2H), 2.02-2.14 (m, 1H), 2.46 (s, 3H), 3.30-3.62 (m, 3H), 3.64-3.72 (m, 1H), 3.79-3.84 (m, 1H), 3.88-3.94 (m, 1H), 4.27-4.38 (m, 1H), 7.53 (t, 1H, J = 7.5 Hz), 7.61 (app t, 1H), 7.69-7.83 (m, 1H), 8.12 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 8.1 Hz), 9.47 (br s, 1H), 12.8 (br s, 1H).	514.2

TABLE IIA-continued

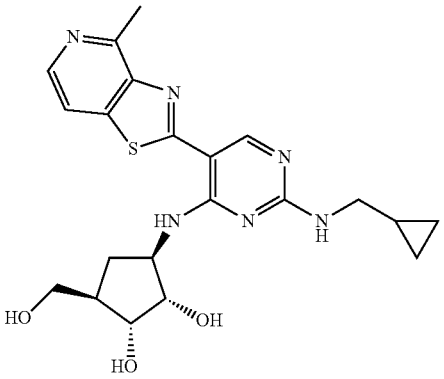
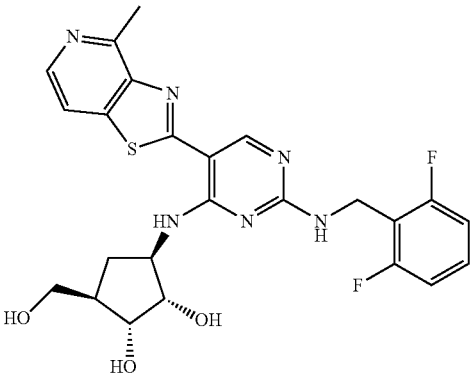
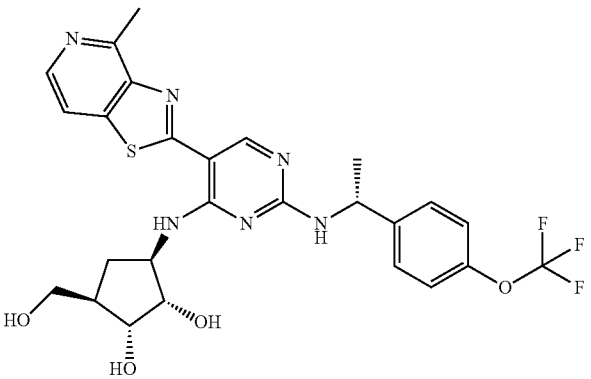
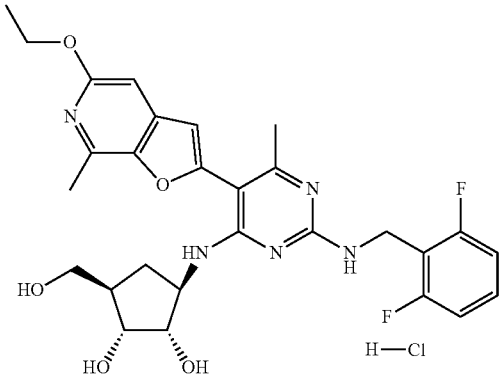
Compd #	Structure	1H NMR data	MS (M + H)+
2531		(DMSO-d6) δ 0.32 (d, 2H, J = 4.1 Hz), 0.51 (d, 2H, J = 7.6 Hz), 1.09-1.20 (m, 1H), 1.22-1.33 (m, 1H), 1.98-2.10 (m, 1H), 2.40-2.49 (m, 2H), 3.05 (s, 3H), 3.39-3.40 (m, 2H), 3.43 (s, 1H), 3.44 (s, 1H), 3.80 (t, 1H, J = 4.4 Hz), 3.90 (t, 1H, J = 5.6 Hz), 4.31-4.40 (quint, 1H, J = 7.1 Hz), 8.51 (d, 1H, J = 6.1 Hz), 8.59 (d, 1H, J = 6.2 Hz), 8.64 (br s, 1H), 8.85 (s, 1H), 9.97-10.05 (m, 1H).	443.2
2532		(DMSO-d6) δ 1.11-1.25 (m, 1H), 1.95-2.11 (m, 1H), 2.30-2.48 (m, 1H), 3.04 (s, 3H), 3.43 (s, 1H), 3.44 (s, 1H), 3.81 (app t, 1H, J = 4.4 Hz), 3.84-3.92 (m, 1H), 4.36-4.48 (quint, 1H, J = 7.3 Hz), 4.70 (dd, 1H, J = 5.1, 14.9 Hz), 4.79 (dd, 1H, J = 5.3, 14.5 Hz), 7.13 (t, 2H, J = 8.0 Hz), 7.43 (app quint, 1H), 8.48-8.54 (m, 1H), 8.55 (app d, 1H, J = 6.2 Hz), 8.78 (br s, 1H), 8.78-8.84 (m, 1H), 9.94 (br s, 1H).	515.2
2533		(DMSO-d6) δ 0.92-1.01 (m, 1H), 1.46-1.52 (m, 2H), 1.53 (d, 2H, J = 7.1 Hz), 1.86-2.03 (m, 2H), 3.01 (s, 3H), 3.30-3.46 (m, 2H), 3.74-3.86 (m, 2H), 4.23-4.34 (m, 1H), 5.14-5.24 (app quint, 1H, 7.34 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.8 Hz), 8.50 (d, 1H, J = 6.0 Hz), 8.57 (d, 1H, J = 6.2 Hz), 8.77 (s, 1H), 9.04 (br s, 1H), 9.70 (br s, 1H).	577. 2
2535		(DMSO-d6) δ 1.02-1.11 (m, 1H), 1.33 (t, 3H, J = 7.0 Hz), 1.90-1.95 (m, 1H), 1.98-2.07 (m, 1H), 2.25 (s, 3H), 2.58 (s, 3H), 3.30-3.40 (m, 2H), 3.67 (t, 1H, J = 5.1 Hz), 3.81 (t, 1H, J = 6.4 Hz), 4.31 (q, 2H, J = 7.0 Hz), 4.68 (dd, 1H, J = 5.3, 13.9 Hz), 4.82 (app dd, 1H, J = 6.3, 15.1 Hz), 6.93 (s, 1H), 7.06 (s, 1H), 7.08-7.18 (m, 2H), 7.40-7.48 (m, 1H), 8.03 (d, J = 7.6 Hz), 13.24 (br s, 1H).	556.2

TABLE IIA-continued

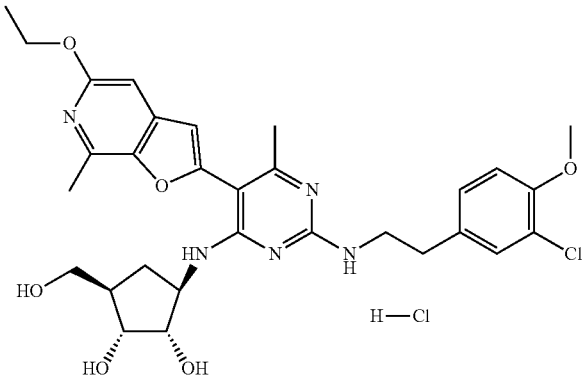
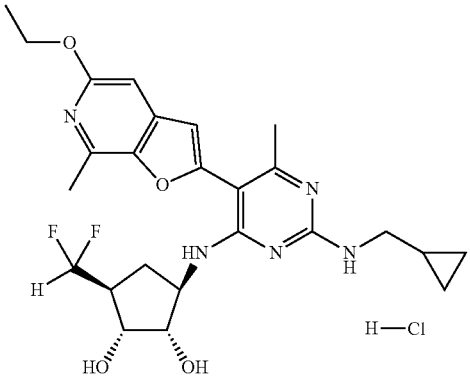
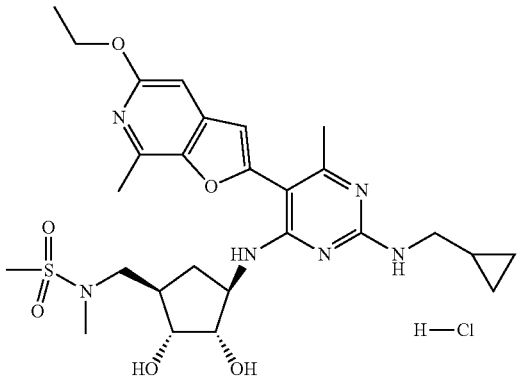
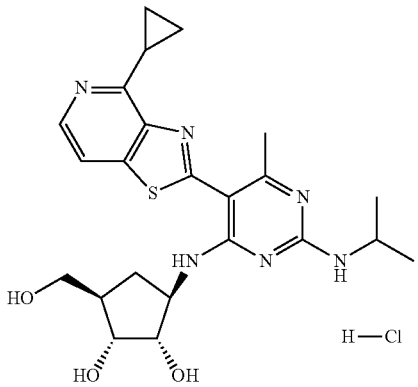
Compd #	Structure	1H NMR data	MS (M + H)+
2536		(DMSO-d6) δ 1.12-1.25 (m, 1H), 1.34 (t, 3H, J = 7.1 Hz), 1.96 (br s, 1H), 2.11-2.21 (m, 1H), 2.26 (s, 3H), 2.59 (s, 3H), 2.62-2.92 (m, 2H), 3.30-3.42 (m, 2H), 3.54-3.70 (m, 2H), 3.67-3.75 (m, 1H), 3.76-3.90 (m, 1H), 3.83 (s, 3H), 4.28-4.39 (m, 2H), 4.45-4.55 (m, 1H), 6.94 (s, 1H), 7.08-7.12 (m, 2H), 7.27 (dd, 1H, J = 6.5, 8.5 Hz), 7.37 (br s, 1H), 7.93-8.05 (m, 2H), 13.22 (br s, 1H).	598.2
2537		(DMSO-d6) δ 0.29-0.34 (m, 2H), 0.48-0.53 (m, 2H), 1.08-1.18 (m, 1H), 1.33 (t, 3H, J = 7.1 Hz), 1.35-1.47 (m, 1H), 2.08-2.18 (m, 1H), 2.27 (s, 3H), 2.27-2.40 (m, 1H), 2.58 (s, 3H), 3.17 (s, 1H), 3.30-3.39 (m, 3H), 3.78-3.86 (m 1H), 4.31 (q, 2H, J = 7.0 Hz), 4.38-4.53 (m, 1H), 6.07 (dt, 1H, J = 3.7, 56.6 Hz), 6.90 (s, 1H), 7.06 (s, 1H), 7.95-8.04 (m, 1H), 8.03 (br s, 1H), 13.10 (br s, 1H).	504.2
2539		(DMSO-d6) δ 0.29-0.33 (m, 2H), 0.47-0.53 (m, 2H), 1.04-1.18 (m, 2H), 1.33 (t, 3H, J = 7.1 Hz), 2.05-2.20 (m, 2H), 2.26 (s, 3H), 2.58 (s, 3H), 2.74 (s, 3H), 2.82 (s, 3H), 2.89 (dd, 1H, J = 7.7, 13.1 Hz), 3.09 (dd, 1H, J = 7.0, 13.2 Hz), 3.28-3.39 (m, 2H), 3.60 (t, 1H, J = 5.1 Hz), 3.83-3.88 (m, 1H), 4.31 (q, 2H, J = ~7.0 Hz), 4.40-4.50 (m, 1H), 6.90 (s, 1H), 7.06 (s, 1H), 7.96-8.03 (m, 1H), 13.10 (br s, 1H).	575.3
2540		(DMSO-d6) δ 1.11-1.39 (m, 11H), 1.45 (br s, 2H), 1.90-2.00 (m, 1H), 2.18-2.30 (m, 1H), 2.45 (s, 3H), 2.98-3.07 (m, 1H), 3.30-3.39 (m, 2H), 3.68 (t, 1H, J = 4.8 Hz), 3.70-3.76 (app t, 1H), 4.33-4.44 (app quint, 1H), 8.08 (br s, 1H), 8.22-8.29 (m, 1H), 8.47 (d, 1H, J = 5.9 Hz), 9.07 (br s, 1H), 13.37 (br s, 1H).	471.2

TABLE IIA-continued

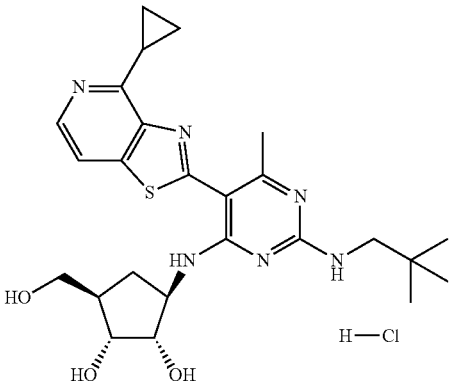
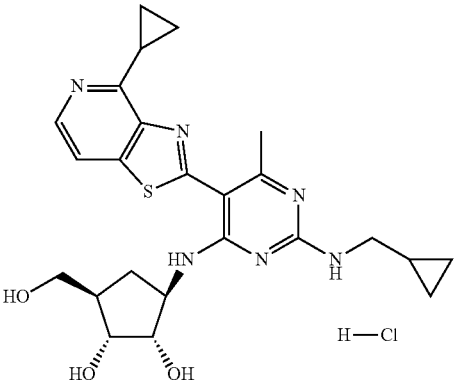
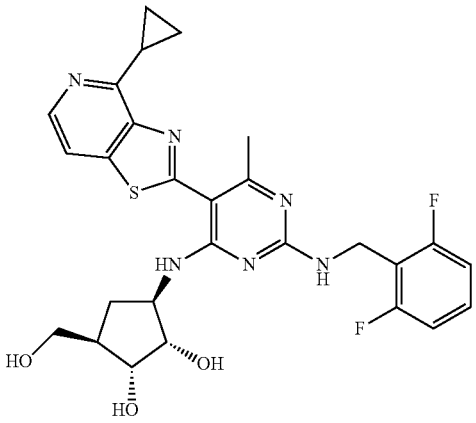
Compd #	Structure	1H NMR data	MS (M + H)+
2541		(DMSO-d6) δ 0.98 (s, 9H), 1.13-1.25 (m, 2H), 1.28-1.35 (m, 2H), 1.45 (br s, 2H), 1.90-2.00 (m, 1H), 2.18-2.30 (m, 1H), 2.47 (s, 3H), 2.98-3.06 (m, 1H), 3.28-3.40 (m, 4H), 3.68 (t, 1H, J = 4.9 Hz), 3.76-3.81 (m, 1H), 4.33-4.43 (m, 1H), 8.15-8.28 (m, 1H), 8.29-8.36 (m, 1H), 8.46 (d, 1H, J = 5.8 Hz), 9.08 (br s, 1H), 13.60 (br s, 1H).	499.2
2542		(DMSO-d6) δ 0.29-0.37 (m, 2H), 0.48-0.54 (m, 2H), 1.09-1.25 (m, 3H), 1.26-1.34 (m, 2H), 1.42 (br s, 2H), 1.91-2.00 (m, 1H), 2.18-2.30 (m, 2H), 2.46 (s, 3H), 2.98-3.07 (m, 1H), 3.29-3.42 (m, 5H), 3.68 (app t, 1H, J = 4.8 Hz), 3.77 (app t, 1H, J = 6.0 Hz), 4.36-4.46 (app quint, 1H), 8.12 (br s, 1H), 8.21-8.28 (m, 1H), 8.46 (d, 1H, J = 5.7 Hz), 9.06 (br s, 1H), 13.38 (br s, 1H).	483.2
2543		(DMSO-d6) δ 1.01-1.12 (m, 1H), 1.22-1.34 (m, 3H), 1.40 (br s, 2H), 1.92-2.03 (m, 1H), 2.08-2.18 (m, 1H), 2.42 (s, 3H), 2.97-3.06 (m, 1H), 3.31-3.41 (m, 3H), 4.42-4.53 (quint, 1H, J = 7.8 Hz), 4.71 (dd, 1H, J = 5.2, 14.8 Hz), 4.83 (dd, 1H, J = 6.0, 14.9 Hz), 7.10-7.19 (m, 2H), 7.40-7.49 (m, 1H), 8.18-8.25 (m, 1H), 8.36-8.54 (br s, 1H), 8.45 (d, 2H, J = 5.7 Hz), 9.04 (br s, 1H).	555.2

TABLE IIA-continued

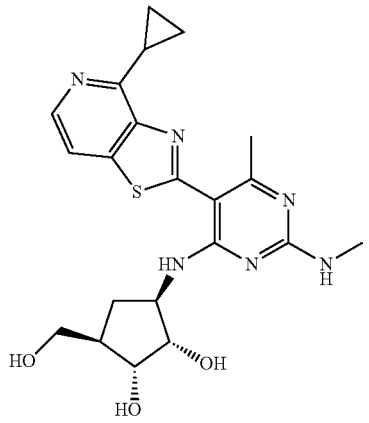
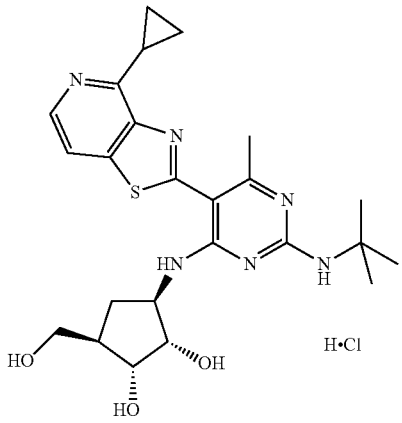
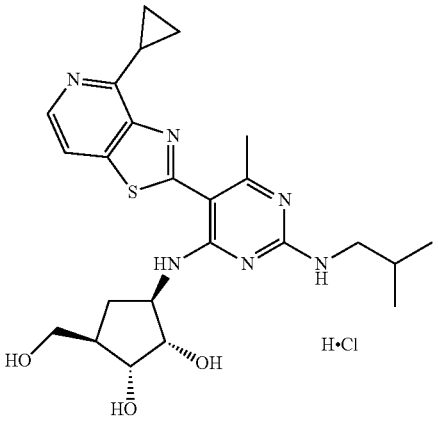
Compd #	Structure	1H NMR data	MS (M + H)+
2544		(DMSO-d6) δ 1.11-1.26 (m, 2H), 1.30-1.39 (m, 2H), 1.49 (br s, 2H), 1.95 (br s, 1H), 2.19-2.32 (m, 1H), 2.46 (s, 3H), 3.00 (d, 3H, J = 4.5 Hz), 2.97-3.08 (m, 1H), 3.30-3.40 (m, 2H), 3.65 (m, 2H), 4.38-4.49 (m, 1H), 7.92 (br s, 1H), 8.27-8.32 (m, 1H), 8.47 (d, 1H, J = 5.5 Hz), 9.02 (br s, 1H).	443.2
2545		(DMSO-d6) δ 1.14-1.27 (m, 2H), 1.29-1.36 (m, 2H), 1.42-1.52 (m, 1H), 1.48 (s, 9H), 1.90-2.01 (m, 1H), 2.19-2.30 (m, 1H), 2.43 (s, 3H), 2.97-3.06 (m, 1H), 3.30-3.40 (m, 2H), 3.70 (t, 1H, J = 4.8 Hz), 3.76-3.81 (m, 1H), 4.41 (quint, 1H, J = ~7.6 Hz), 8.18 (br s, 1H), 8.24-8.30 (m, 1H), 8.47 (d, 1H, J = 6.0 Hz), 9.06 (br s, 1H).	485.2
2546		(DMSO-d6) δ 0.95 (s, 3H), 0.97 (s, 3H), 1.10-1.24 (m, 1H), 1.30-1.38 (m, 2H), 1.49 (br s, 2H), 1.87-2.01 (m, 2H), 2.18-2.30 (m, 1H), 2.46 (s, 3H), 2.99-3.08 (m, 1H), 3.24-3.40 (m, 4H), 3.68 (t, 1H, J = 4.8 Hz), 3.65-3.81 (m, 1H), 4.37 (quint, 1H, J = 7.4 Hz), 8.23-8.33 (m, 2H), 8.47 (d, 1H, J = 5.9 Hz), 9.03 (br s, 1H).	485.2

TABLE IIA-continued

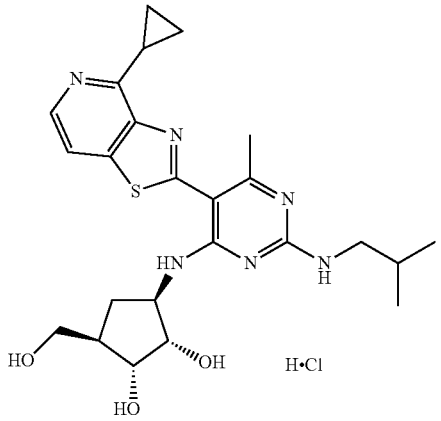
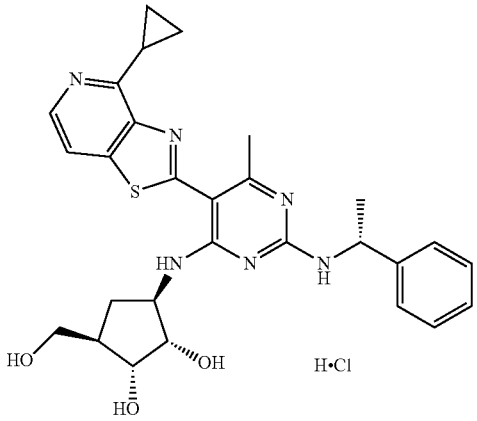
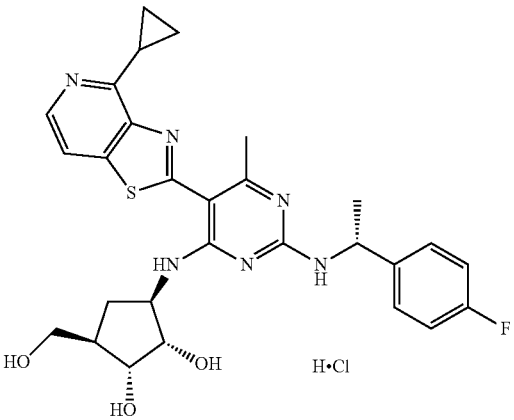
Compd #	Structure	1H NMR data	MS (M + H)+
2547		(DMSO-d6) δ 1.12-1.24 (m, 2H), 1.21 (t, 3H, J = 7.2 Hz), 1.26-1.34 (m, 2H), 1.42 (br s, 2H), 1.94 (br s, 1H), 2.17-2.30 (m, 1H), 2.45 (s, 3H), 2.98-3.07 (m, 1H), 3.29-3.39 (m, 2H), 3.43-3.55 (m, 3H), 3.65-3.82 (t, 1H, J = 4.8 Hz), 3.74-3.83 (m, 1H), 4.40 (quint, 1H, J = 7.5 Hz), 8.03 (br s, 1H), 8.19-8.26 (m, 1H), 8.46 (d, 1H, J = 5.9 Hz), 9.05 (br s, 1H).	457.2
2549		(DMSO-d6) δ 0.85-0.97 (m, 1H), 1.18-1.24 (m, 2H), 1.30 (br s, 2H), 1.55 (d, 3H, J = 7.1 Hz), 1.66-1.78 m, 1H), 1.84-1.95 (m, 1H), 2.41 (s, 3H), 2.94-3.02 (m, 1H), 3.25-3.35 (m, 2H), 4.32-4.44 (m, 1H), 5.10-5.20 (m, 1H), 7.24-7.30 (app t, 1H), 7.37 (app t, 2H, J = 7.6 Hz), 7.45 (d, 2H, J = 7.4 Hz), 8.08-8.15 (m, 1H, J = 5.0 Hz), 8.42 (d, 1H, J = 5.6 Hz), 8.60-8.65 (m, 1H), 9.01 (br s, 1H).	533.2
2550		(DMSO-d6) δ 0.88-1.00 (m, 1H), 1.22-1.32 (m, 3H), 1.40 (br s, 2H), 1.54 (d, 3H, J = 6.9 Hz), 1.65-1.77 m, 1H), 1.85-1.96 (m, 1H), 2.42 (s, 3H), 2.94-3.02 (m, 1H), 3.27-3.36 (m, 2H), 3.64-3.69 (m, 1H), 3.69-3.75 (m, 1H), 4.36 (quint, 1H, J = 7.8 Hz), 5.10-5.21 (m, 1H), 7.19 (t, 2H, J = 8.9 Hz), 7.45-7.53 (m, 2H), 8.17-8.25 (m, 1H), 8.45 (d, 1H, J = 5.6 Hz), 8.70-8.78 (m, 1H), 8.94 (br s, 1H).	551.2

TABLE IIA-continued

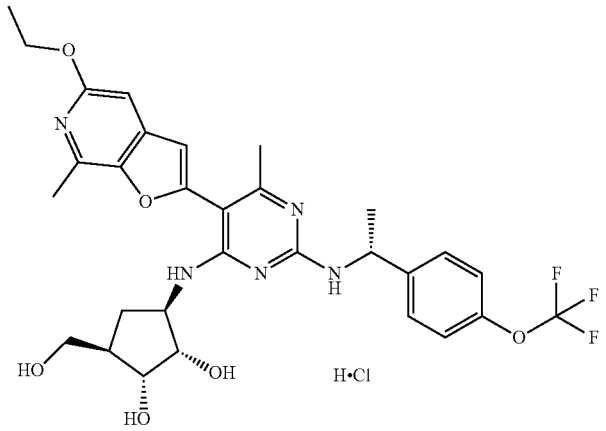
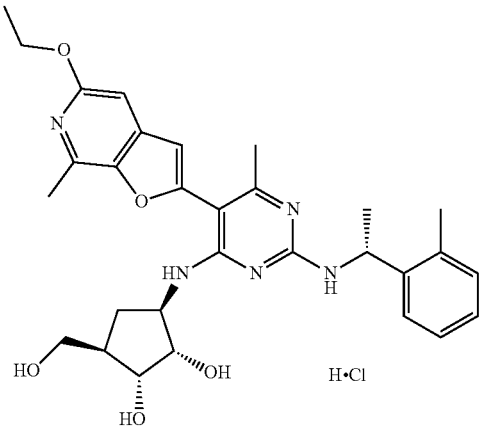
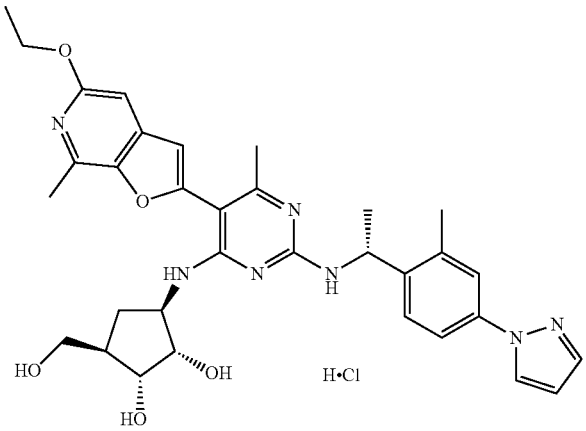
Compd #	Structure	1H NMR data	MS (M + H)+
2553			618.3
2555		(DMSO-d6) δ 0.75-0.90 (m, 1H), 1.34 (t, 3H, J = 6.9 Hz), 1.47 (d, 4H, J = 6.9 Hz), 1.76-1.87 (m, 1H), 2.27 (s, 3H), 2.42 (s, 3H), 2.59 (s, 3H), 3.21-3.32 (m, 2H), 3.62-3.77 (m, 1H), 3.73-3.78 (m, 1H), 4.32 (quart, 2H, J = 7.0 Hz), 5.29 (quint, 1H, J = 6.9 Hz), 7.00 (s, 1H), 7.08 (s, 1H), 7.11-7.24 (m, 3H), 7.35 (d, 1H, J = 7.7 Hz), 8.00 (d, 1H, J = 7.8 Hz), 8.88 (d, 1H, J = 6.9 Hz), 13.35 (br s, 1H).	
2556		(DMSO-d6) δ 0.50-1.05 (m, 1H), 1.32 (dt, 3H, J = 7.0, 2.0 Hz), 1.53-1.68 (m, 1H), 1.57 (d, 3H, J = 6.8 Hz), 1.84-1.93 (app octet, 1H), 2.25 (s, 3H), 2.55 (s, 3H), 3.22-3.39 (m, 2H), 3.65 (t, 1H, J = 5.1 Hz), 3.70-3.78 (m, 2H), 4.25-4.32 (m, app quart, 2H), 4.34-4.45 (m, app quint, 1H), 5.10-5.19 (m, 1H), 6.53 (t, 1H, J = 2.3 Hz), 6.86 (s, 1H), 7.01 (s, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.72-7.75 (m, 1H), 7.80-7.86 (m, 2H), 7.98 (m, 1H), 8.45-8.48 (m, 1H), 8.52-8.60 (m, 1H), 12.88 (br s, 1H).	600.3

TABLE IIA-continued

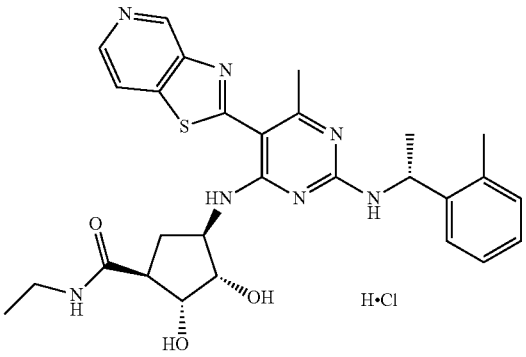
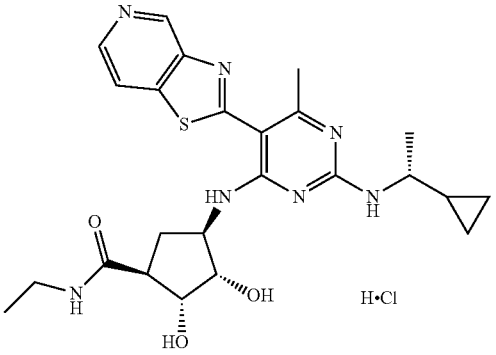
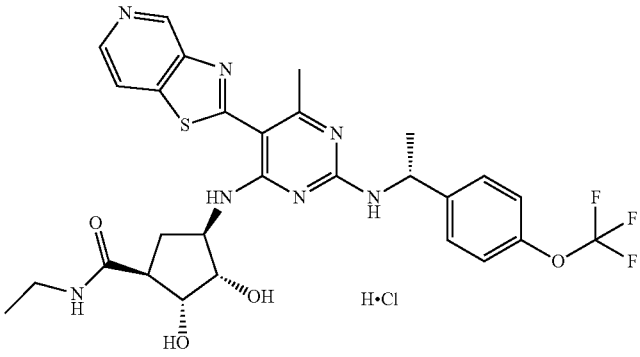
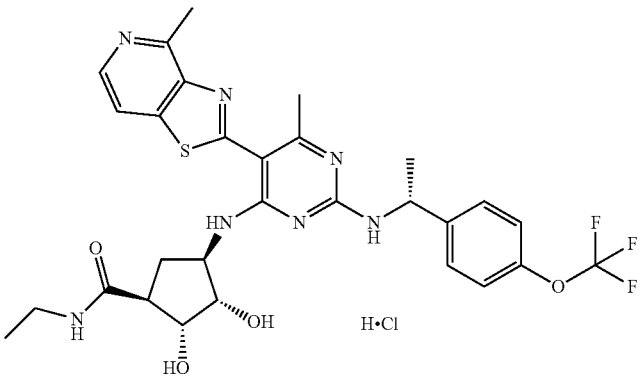
Compd #	Structure	1H NMR data	MS (M + H)+
2559		(DMSO-d6) δ 0.96 (t, 3H, J = 7.3 Hz), 1.18-1.29 (m, 1H), 1.50 (d, 3H, 6.8 Hz), 1.70-1.82 (m, 1H), 2.42 (s, 3H), 2.45 (s, 3H), 2.90-3.01 (m, 2H), 3.75-3.90 (m, 2H), 4.22-4.32 (m , 1H), 5.34 (m, app quint, 1H, J = 7.0 Hz), 7.14 (app t, 1H, J = 7.2 Hz), 7.18-7.25 (m, 2H), 7.38 (d, 1H, J = 7.4 Hz), 7.99 (t, 1H, J = 5.5 Hz), 8.54 (d, 1H, J = 5.8 Hz), 8.69 (d, 1H, J = 5.8 Hz), 8.80 (d, 1H, J = 6.9 Hz), 9.19 (d, 1H, J = 7.2 Hz), 9.63 (s, 1H).	548.2
2562		(DMSO-d6) δ 0.28-0.36 (m, 1H), 0.0.37-0.45 (m, 1H), 0.45-0.59 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz), 1.02-1.13 (m, 1H), 1.32 (d, 3H, J = 6.5 Hz), 1.47-1.57 (m, 1H), 2.25-2.37 (m, 1H), 2.48 (s, 3H), 2.57-2.66 (m, 1H), 2.87-2.98 (m, 2H), 3.60-3.72 (m, 1H), 3.80-3.86 (m, 1H), 3.92 (t, 1H, J = 5.1 Hz), 4.35 (br s, 1H), 8.02-8.10 (m, 1H), 8.24-8.35 (m, 1H), 8.73 (d, 1H, J = 5.9 Hz), 8.78 (d, 1H, J = 6.1 Hz), 9.38-9.48 (m, 1H), 9.80 (s, 1H).	498.2
2563		(DMSO-d6) δ 0.96 (t, 3H, J = 7.2 Hz), 1.22-1.35 (m, 1H), 1.55 (d, 3H, J = 6.8 Hz), 1.76-1.88 (m, 1H), 2.42 (s, 3H), 2.52-2.60 (m, 1H), 2.89-3.02 (m, 2H), 3.82 (t, 1H, J = 5.1 Hz), 3.87 (t, 1H, J = 5.4 Hz), 4.23-4.33 (m, 1H), 5.15-5.25 (m, 1H), 7.39 (d, 2H, J = 8.0 Hz), 7.59 (d, 1H, J = 8.6 Hz), 8.01 (app t, 1H, J = 5.5 Hz), 8.53 (d, 1H, J = 5.7 Hz), 8.69 (d, 1H, J = 5.9 Hz), 8.71-8.79 (m, 1H), 9.18-9.25 (m, 1H), 9.63 (s, 1H).	618.2
2564		(DMSO-d6) δ 0.94 (t, 3H, J = 7.3 Hz), 1.19-1.29 (m, 1H), 1.55 (d, 3H, J = 7.1 Hz), 1.78-1.90 (m, 1H), 2.46 (s, 3H), 2.85-2.98 (m, 2H), 3.03 (s, 3H), 3.80-3.88 (m, 3H), 4.25 (br s, 1H), 5.14-5.25 (m, 1H), 7.39 (d, 2H, J = 8.3 Hz), 7.58 (d, 2H, J = 8.6 Hz), 7.99 (app t, 1H, J = 5.3 Hz), 8.43-8.51 (m, 1H), 8.59 (d, 1H, J = 6.1 Hz), 8.70-8.80 (m, 1H), 9.10-9.20 (m, 1H).	632.2

TABLE IIA-continued

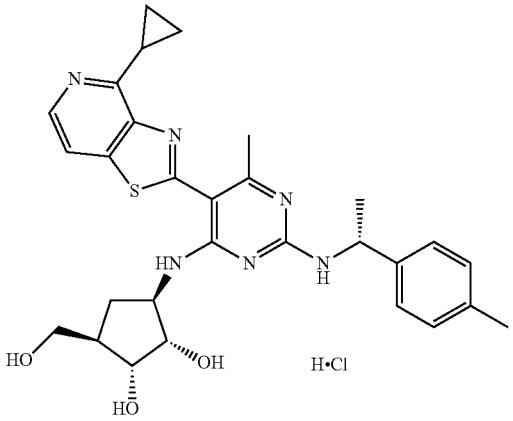
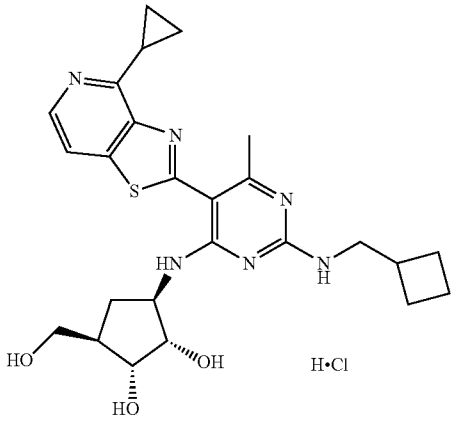
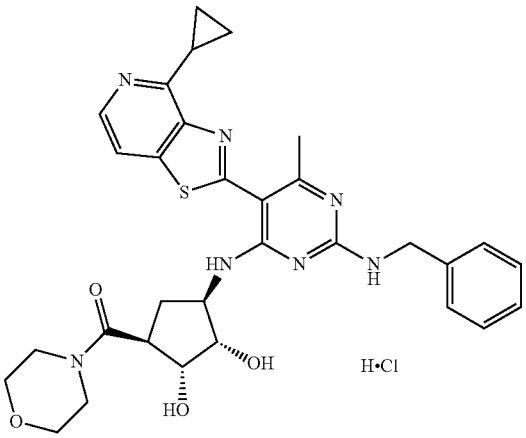
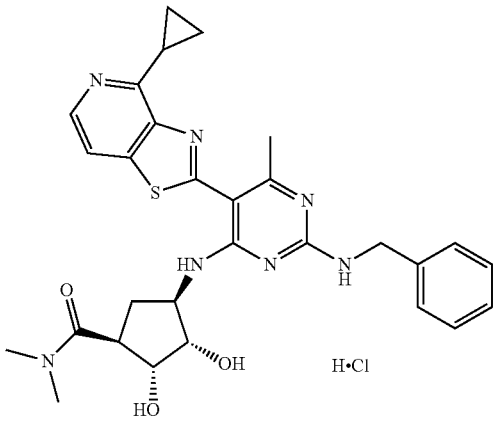
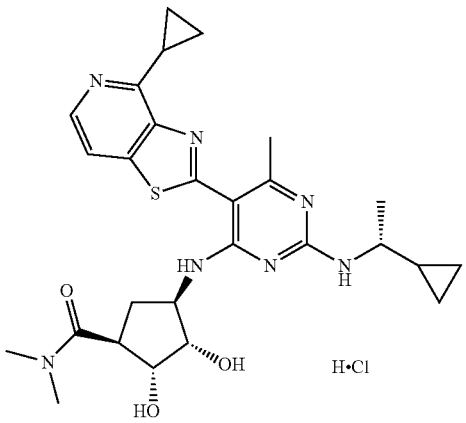
Compd #	Structure	1H NMR data	MS (M + H)+
2565		(DMSO-d6) δ 0.89-0.99 (m, 1H), 1.32-1.42 (m, 2H), 1.48-1.64 (m, 3H), 1.52 (d, 3H, J = 7.0 Hz), 1.71-1.83 (m, 1H), 1.86-1.96 (m or app oct, 1H, J = 4.3 Hz), 2.28 (s, 3H), 2.29-2.40 (m, 1H), 2.42 (s, 3H), 2.98-3.07 (m, 1H), 3.26-3.36 (m, 2H), 3.65-3.70 (app t, 1H), 3.71-3.76 (app t, 1H), 4.37 (quint, 1H, J = 7.7 Hz), 5.06-5.17 (app quint, 1H), 7.18 (d, 2H, J = 8.1 Hz), 7.20-7.45 (m, 1H), 7.32 (d, 2H, J = 7.9 Hz), 8.32-8.38 (m, 1H), 8.48 (d, 1H, J = 6.0 Hz), 8.80-8.88 (m, 2H).	547.2
2566		(DMSO-d6) δ 1.13-1.25 (m, 1H), 1.30-1.38 (m, 2H), 1.49 (br s, 2H), 1.72-1.83 (m, 2H), 1.83-1.93 (m, 1H), 1.92-2.10 (m, 3H), 2.16-2.30 (m, 1H), 2.45 (s, 3H), 2.61 (quint, 1H, J = 7.3 Hz), 3.00-3.08 (m, 1H), 3.30-3.40 (m, 2H), 3.45-3.60 (m, 2H), 3.68 (app t, 1H, J = 6.7 Hz), 3.76-3.82 (m, 1H), 4.34-4.44 (m, 1H), 8.17-8.25 (m, 1H), 8.25-8.35 (m, 1H), 8.47 (d, 1H, J = 6.1 Hz), 9.03 (br s, 1H).	497.2
2567		(DMSO-d6) δ 1.07-1.18 (m, 4H), 1.38-1.63 (m, 1H), 2.30-2.42 (m, 1H), 2.57 (s, 3H), 2.96-3.09 (m, 2H), 3.37-3.62 (m, 7H), 3.74-3.81 (m, 1H), 3.97-4.05 (m, 1H), 4.31-4.51 (m, 2H), 4.56-4.67 (m, 1H), 4.77-4.85 (m, 1H), 4.85-4.94 (m, 1H), 7.18-7.26 (m, 1H), 7.31 (t, 2H, J = 7.6 Hz), 7.34-7.41 (m, 2H), 7.83-7.95 (m, 1H), 7.86 (d, 1H, J = 5.5 Hz), 8.28 (d, 1H, J = 5.2 Hz), 9.58-9.88 (m, 1H).	602.3

TABLE IIA-continued

Compd #	Structure	1H NMR data	MS (M + H)+
2568		(DMSO-d6) δ 1.15-1.27 (m, 3H), 1.28-1.36 (m, 2H), 1.39-1.49 (m, 1H), 2.14-2.25 (m, 1H), 2.42 (s, 3H), 2.63 (s, 3H), 2.96-3.10 (m, 1H), 2.99 (s, 3H), 3.80 (t, 2H, J = 5.3 Hz), 3.88 (t, 3H, J = 4.7 Hz), 4.40-4.48 (m, 1H), 4.61-4.75 (m, 2H), 7.22-7.35 (m, 1H), 7.35-7.42 (m, 2H), 7.42-7.50 (m, 2H), 8.10-8.16 (m, 1H), 8.43 (d, 1H, J = 5.7 Hz), 8.45 (br s, 1H), 9.14 (br s, 1H).	
2569		(DMSO-d6) δ 0.26-0.35 (m, 1H), 0.36-0.44 (m, 1H), 0.44-0.57 (m, 2H), 1.01-1.14 (m, 2H), 1.15-1.42 (m, 6H), 1.32 (d, 3H, J = 6.7 Hz), 1.48-1.60 (m, 2H), 2.25-2.40 (m, 2H, 2.43 (s, 3H), 2.64 (s, 3H), 2.96-3.15 (m, 4H), 3.01 (s, 3H), 3.60-3.73 (m, 1H), 3.81 (t, 1H, J = 5.1 Hz), 3.89 (t, 1H, J = 4.8 Hz), 4.31-4.48 (m, 1H), 8.10-8.24 (m, 1H), 8.41-8.48 (m, 1H), 9.21 (br s, 1H).	538.3

HCV Replicon assay data for compounds of the invention shown in Table IIB that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIB as a falling within the following range: "B"—greater than about 0.5 μM to less than or equal to about 5.0 μM

TABLE IIB

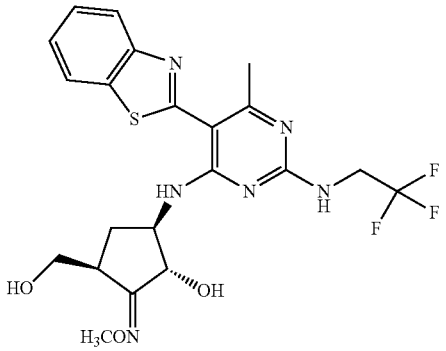
Compd #	Structure	1H NMR data	MS (M + H)+
2503		(DMSO-d6, mixture of isomers) δ 1.57-1.72 (m, 1H), 2.31-2.48 (m, 1H), 2.45-2.75 (m, 3H), 2.86 and 2.98 (br s's, 1H) 3.56-3.3.68 (m, 1H), 3.64-3.75 (m, 1H), 3.73 and 3.79 (s, 3H), 4.03-4.42 (4 m, 4H), 4.60-4.75 (m, 1H), 5.31-5.37 and (m and d, 1H, doublet's J = 6.3 Hz), 7.40-7.47 (m, 1H), 7.50-7.57 (m, 1H), 7.77 (br s, 1H), 8.02-8.08 (m, 1H), 8.08-8.14 (m, 1H, 9.42-9.62 (m, 1H).	497.2

TABLE IIB-continued

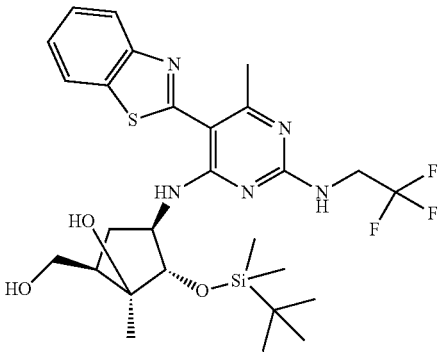
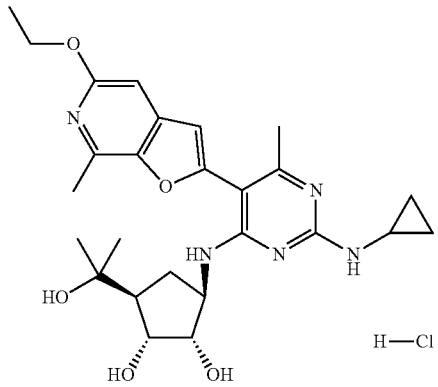
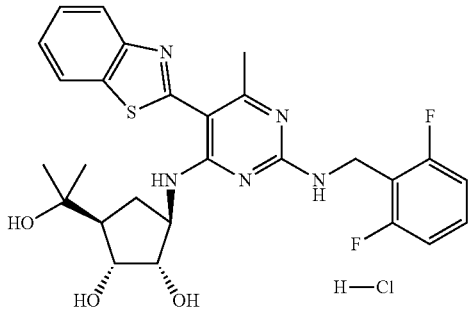
Compd #	Structure	1H NMR data	MS (M + H)+
2507		NMR spectrum not available; ID determined by MS and from the NMR spectrum for its director precursor (SRI 25595).	484.2
2517		(DMSO-d6) δ 0.67 (br s, 2H), 0.82-0.89 (m, 2H), 1.01 (s, 3H), 1.11 (s, 3H), 1.23-1.38 (m, 1H), 1.33 (t, 3H, J = 7.0 Hz), 1.64-1.78 (m, 1H), 1.84-2.05 (m, 1H), 2.29 (s, 3H), 2.58 (s, 3H), 2.78-2.88 (m 1H), 3.50-3.80 (m, 2H), 4.30 (app q, 2H, J = 7.1 Hz), 4.35-4.50 (m, 1H), 6.89 (s, 1H), 7.05 (s, 1H), 8.01 (br s, 2H).	498.3
2522		(DMSO-d6) δ 1.03 (s, 3H), 1.16 (s, 3H), 1.15-1.26 (m, 1H), 1.79-1.90 (m, 1H), 1.89-2.01 (m, 1H), 2.42 (s, 3H), 3.62-3.71 (m, 1H), 3.83 (dd, 1H, J = 3.7, 6.3 Hz), 4.34-4.46 (m, 1H), 4.66 (app dd, 1H, J = 5.4, 15.3 Hz), 4.76-4.86 (m, 1H), 7.08-7.16 (m, 2H), 7.38-7.46 (m, 1H), 7.53 (app t, 1H, J = 7.5 Hz), 7.57-7.63 (m, 1H), 8.11 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 8.0 Hz), 8.21-8.35 (m, 1H), 12.93 (br s, 1H).	542.2

TABLE IIB-continued

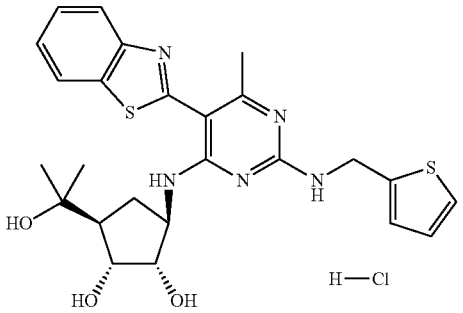
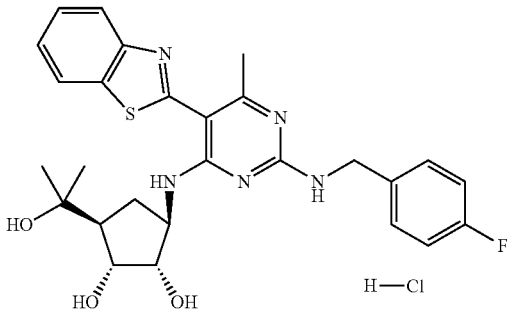
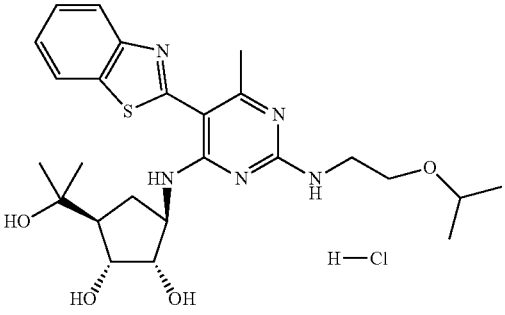
Compd #	Structure	1H NMR data	MS (M + H)+
2523		(DMSO-d6) δ 1.02 (s, 3H), 1.14 (s, 3H), 1.22-1.31 (m, 1H), 1.78 (dt, 1H, J = 4.0, 9.8 Hz), 1.94-2.04 (m, 1H), 2.45 (br s, 3H), 3.64-3.70 (m, 1H), 3.82 (dd, 1H, J = 3.9, 5.8 Hz), 4.40-4.52 (m, 1H), 4.75 (app dd, 1H, J = 5.8, 15.3 Hz), 4.87 (dd, 1H, J = 5.9, 15.2 Hz), 6.99 (dd, 1H, J = 3.5, 5.1 Hz), 7.13 (br d, 1H, J = 2.9 Hz), 7.44 (app dd, 1H, J = 1.0, 5.1 Hz), 7.50-7.56 (m, 1H), 7.58-7.63 (m, 1H), 8.12 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 8.1 Hz), 8.31 (br s, 1H), 13.06 (br s, 1H).	512.2
2524		(DMSO-d6) δ 0.98 (s, 3H), 1.13 (s, 3H), 1.13-1.26 (m, 1H), 1.69-1.85 (m, 1H), 2.45 (s, 3H), 3.63 (dd, 1H, J = 6.0, 8.6 Hz), 3.78-3.82 (m, 1H), 4.28-4.38 (m, 1H), 4.54-4.67 (m, 2H), 7.18 (t, 2H, J = 8.8 Hz), 7.45 (dd, 1H, J = 5.6, 8.4 Hz), 7.53 (t, 1H, J = 7.5 Hz), 7.57-7.63 (m, 1H), 8.11 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 7.8 Hz), 8.34 (br s, 1H), 13.13 (br s, 1H).	524.2
2525		(DMSO-d6) δ 1.03 (s, 3H), 1.12 (d, 6H, J = 6.1 Hz), 1.14 (s, 3H), 1.26-1.38 (m, 1H), 1.69-1.82 (m, 1H), 2.02-2.12 (m, 1H), 2.46 (s, 3H), 3.50-3.72 (m, 7H), 3.80-3.82 (m, 1H), 4.35 (quint, 1H, J = 8.3 Hz), 7.53 (t, 1H, J = 7.5 Hz), 7.58-7.64 (m, 1H), 7.60-7.73 (m, 1H), 8.12 (d, 1H, J = 8.2 Hz), 8.20 (d, 1H, J = 7.9 Hz), 9.46 (br s, 1H), 12.91 (br s, 1H).	502.2

TABLE IIB-continued

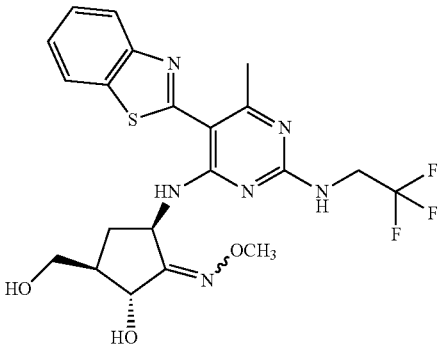
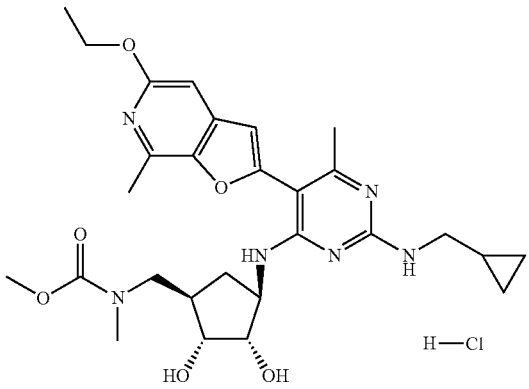
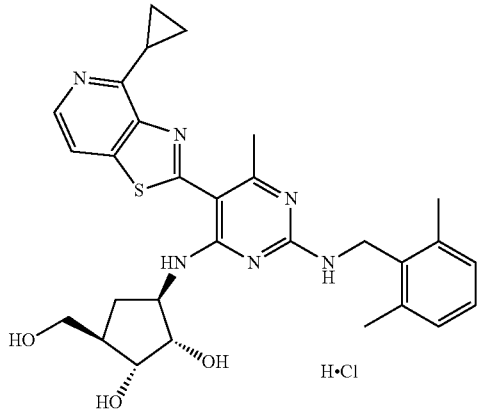
Compd #	Structure	1H NMR data	MS (M + H)+
2534		(DMSO-d6, mix of isomers) δ 1.10-1.25 and 1.40-1.50 (m, 1H), 1.73-1.85 and 1.87- 2.00), m, 1H), 2.38-2.68 (m 1H), 2.45 and 2.62 (s, 3H), 3.42-3.62 (m, 2H), 3.70 and 3.87 (s, 3H), 4.03-4.28 (m, 2H), 4.33 and 4.42 (br s, 1H), 4.52-4.58 and 4.57-4.62 (app t, 1H), 4.88-5.03 (m, 1H), 5.21 and 5.26 (d, 1H, J = 6.2 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.51-7.59 (m, 1H), 7.72 and 7.85 (br s, 1H), 7.92-8.00 (m, 1H), 8.12 (d, 1H, J = 7.8 Hz), 10.04 (br s, 1H),	497.2
2358		(DMSO-d6) δ 0.28-0.33 (m, 2H), 0.47-0.53 (m, 2H), 1.01-1.18 (m, 2H), 1.33 (t, 3H, J = 7.1 Hz), 2.03-2.15 (m, 2H), 2.26 (s, 3H), 2.58 (s, 3H), 2.81 (s, 3H), 3.08 (dd, 1H, J = 7.1, 13.9 Hz), 3.27-.38 (m, 3H), 3.51-3.57 (m, 1H), 3.54 (s, 3H), 3.84-3.90 (m, 1H), 4.31 (app q, 2H, J = ~7.0 Hz), 4.38-4.47 (m, 1H), 6.90 (s, 1H), 7.06 (s, 1H), 7.95-8.04 (m, 1H), 13.08 (br s, 1H).	555.3
2548		(DMSO-d6) δ 1.10-1.24 (m, 6H), 1.23 (s, 1H), 1.98 (br s, 1H), 2.30-2.51 (m, 1H), 2.37 (br s, 6H), 2.51-2.69 (m, 3H), 2.89-2.99 (m, 1H), 3.30-3.46 (m, 2H), 3.61-3.84 (m, 2H), 4.10-4.70 (m, 6H), 7.00-7.10 (m, 3H), 7.11-7.35 (m, 1H), 7.87 (d, 1H, J = 5.5 Hz), 8.29 (d, 1H, J = 5.3 Hz), 9.95 (br s, 1H).	547.2

TABLE IIB-continued

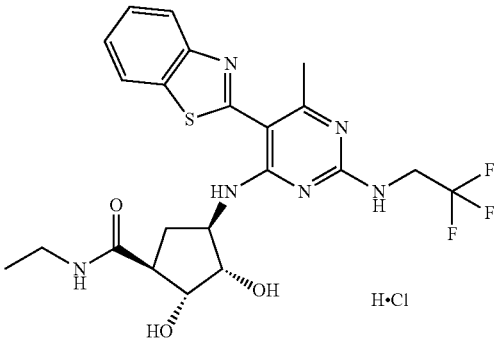
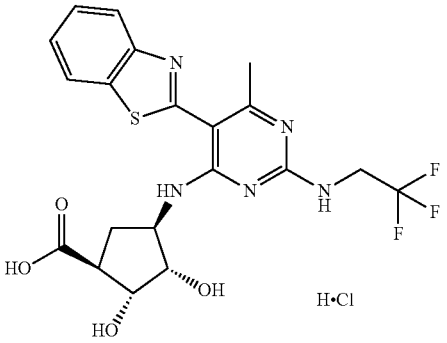
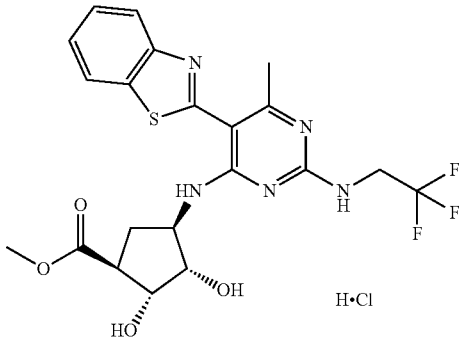
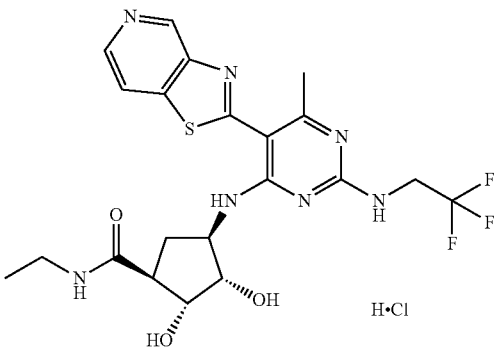
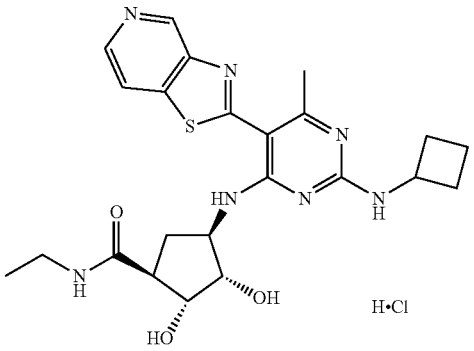
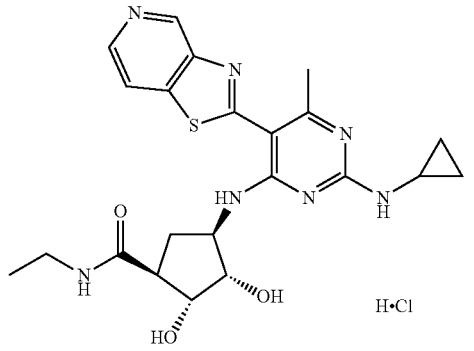
Compd #	Structure	1H NMR data	MS (M + H)+
2552		(DMSO-d6) δ 0.96 (t, 3H, J = 7.3 Hz), 1.49-1.58 (m, 1H), 2.26-2.38 (m, 1H), 2.48 (s, 3H), 2.58-2.68 (m, 1H), 2.99 (quint, 2H, J = 7.0 Hz), 3.84 (t, 1H, J = 4.7 Hz), 3.94 (t, 1H, J = 5.5 Hz), 4.24-4.46 (m, 3H), 7.49-7.66 (m, 3H), 7.87-7.94 (m, 1H), 8.14-8.36 (m, 3H), 9.77 (br s, 1H).	511.2
2554		(DMSO-d6) δ 0.82-0.90 (m, 1H), 1.15-1.32 (m, 2H), 1.55-1.66 (m, 1H), 2.52 (s, 3H), 2.65-2.77 (m, 1H), 3.81-3.87 (m, 1H), 4.04-4.10 (m, 1H), 4.17-4.35 (m, 1H), 4.32-4.47 (m, 2H), 7.46-7.56 (m, 1H), 7.55-7.62 (m, 1H), 8.14 (d, 1H, J = 8.2 Hz), 8.19 (d, 1H, J = 7.8 Hz), 8.10-8.34 (br s, 1H), 9.73 (s, 1H), 12.21 (br s, 1H).	484.1
2557		(DMSO-d6) δ 1.02-1.31 (m, 1H), 1.56-1.67 (m, 1H), 2.65-2.85 (m, 1H), 3.61 (s, 3H), 3.78-3.92 (m, 1H), 4.03-4.10 (m, 1H), 4.17-4.37 (m, 1H), 4.31-4.49 (m, 2H), 7.48-7.56 (m, 1H), 7.56-7.63 (m, 1H), 8.14 (d, 1H, J = 8.0 Hz), 8.19 (d, 1H, J = 8.0 Hz), 9.50-9.80 (m, 1H).	498.1
2558		(DMSO-d6) δ 0.89-0.99 (m, 3H), 1.44-1.58 (m, 1H), 2.26-2.39 (m, 2H), 2.54-2.69 (m, 1H), 2.85-3.02 (m, 2H), 3.75-3.85 (m, 1H), 3.88-3.97 (m, 1H), 4.24-4.46 (m, 3H), 7.97-8.06 (m, 1H), 8.40 (br s, 1H), 8.54-8.60 (m, 1H), 8.68-8.73 (m, 1H), 9.48 (br s, 1H), 9.64-9.71 (m, 1H).	512.2

TABLE IIB-continued

Compd #	Structure	1H NMR data	MS (M + H)+
2560		(DMSO-d6) δ 0.89-0.97 (m, 3H), 1.44-1.59 (m, 2H), 1.68-1.84 (m, 1H), 1.88-2.18 (m, 3H), 2.25-2.43 (m, 2H), 2.44 (s, 3H), 2.53-2.68 (m, 1H), 2.85-2.97 (m, 2H), 3.59-3.74 (m, 3H), 3.80-3.87 (m, 1H), 3.88-3.95 (m, 1H), 4.34-4.53 (m, 2H), 7.95-8.03 (m, 1H), 8.34 (br s, 1H), 8.49-8.57 (m, 1H), 8.70 (d, 1H, J = 5.5 Hz), 9.07 (br s, 1H), 9.39 (br s, 1H, 9.64 (d, 1H, J = 8.8 Hz).	484.2
2561		(DMSO-d6) δ 0.33-0.38 (m, 1H), 0.55-0.61 (m, 1H), 0.60-0.74 (m, 3H), 0.83-1.02 (m, 4H), 0.93 (t, 3H, J = 7.3 Hz), 1.50 (br s, 2H), 1.74 (s, 1H), 2.10-2.50 (m, 4H), 2.45 (s, 3H), 2.55-2.64 (m, 2H), 2.90 (m, 5H), 4.39-4.49 (m, 1H), 4.64 (br s, 1H), 7.88 (br s, 1H), 7.99 (t, 1H, J = 5.4 Hz), 8.05-8.44 (m, 1H), 8.48-8.55 (m, 1H), 8.66-8.72 (m, 1H), 9.55-9.67 (m, 1H).	470.2

HCV Replicon assay data for compounds of the invention shown in Table IIC that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIC as a falling within the following range: "C"—greater than about 5.0 μM to less than or equal to about 25 μM

TABLE IIC

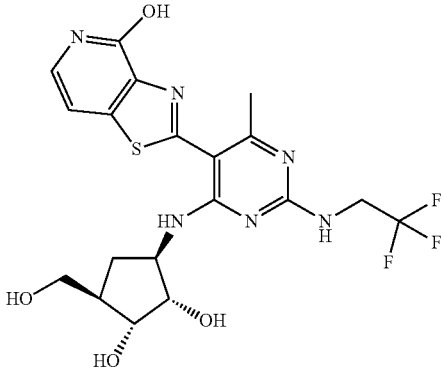
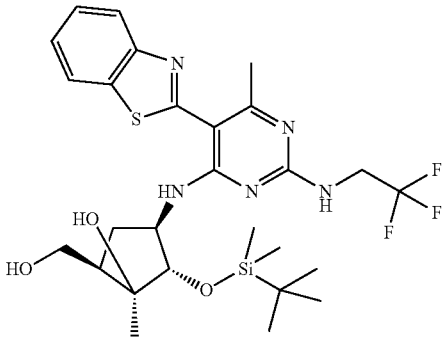
Compd #	Structure	1H NMR data	MS (M + H)+
2501		(DMSO-d6) δ 1.45-1.25 (m, 1H), 1.90-2.20 (m, 1H), 2.23 (dt, 1H, J = 8.7, 13.7 Hz), 2.42 (s, 3H), 3.36-3.46 (m, 2H), 3.69-3.74 (m, 1H), 3.76-3.81 (m, 1H), 4.20-4.35 (m, 1H), 4.33-4.45 (m, 1H), 7.03 (d, 1H, J = 6.9 Hz), 7.43 (t, 1H, J = 6.4 Hz), 8.12-8.28 (br s, 1H), 9.33 (br s, 2H), 11.83-11.93 (m, 1H).	487.1

TABLE IIC-continued

Compd #	Structure	1H NMR data	MS (M + H)+
2506		($CDCl_3$) δ 0.05 (s, 6H), 0.86 (s, 9H), 1.36 (s, 3H), 1.78-1.95 (m, 1H), 2.06-2.17 (m, 1H), 2.30-2.43 (m, 1H), 2.66 (s, 3H), 3.78-3.83 (m, 1H), 3.80-3.97 (m, 1H), 4.01-4.08 (m, 1H), 4.08-4.30 (m, 2H), 3.43-3.61 (m, 1H), 5.2 (br s, 1H), 7.32-7.41 (m, 1H), 7.43-7.51 (m, 1H), 7.87 (d, 1H, J = 7.4 Hz), 7.94 (d, 1H, J = 7.8 Hz), 9.98 (d, 1H, J = 8.4 Hz).	598.2

HCV Replicon assay data for compounds of the invention shown in Table IID that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IID as a falling within the following range: "D"—greater than about 25.0 μM.

TABLE IID

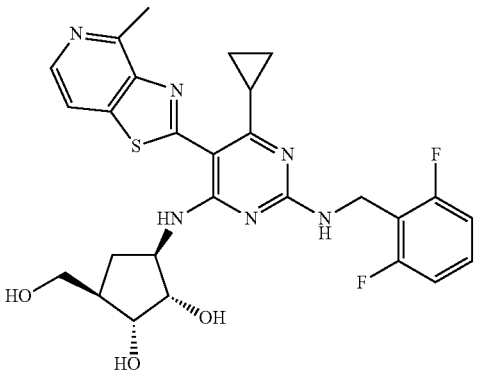
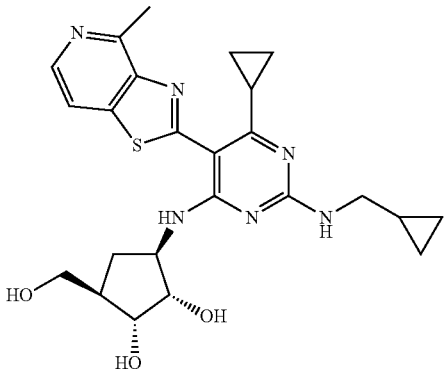
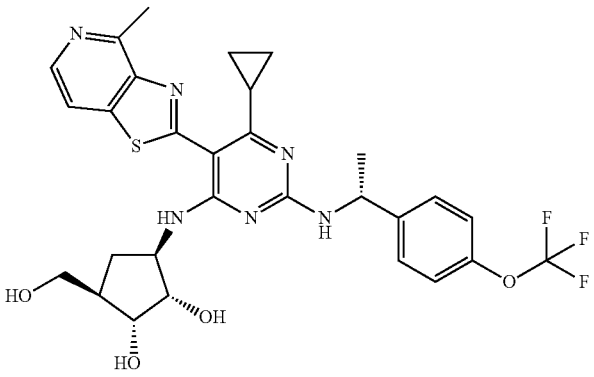
Compd #	Structure	1H NMR data	MS (M + H)+
2528		(DMSO-d6) δ 0.98-1.18 (m, 3H), 1.36 (br s, 2H), 1.93-2.04 (m, 1H), 2.17-2.30 (m, 2H), 3.08 (s, 3H), 3.37 (app d, 2H, J = 5.3 Hz), 3.72 (app t, 1H, J = 4.7 Hz), 3.70-3.96 (m, 1H), 4.39-4.47 (app quint, 1H, J = 7.3 Hz), 4.63-4.71 (m, 1H), 4.74-4.83 (m, 1H), 7.13 (app t, 1H, J = 7.9 Hz), 7.38-7.49 (m, 1H), 8.48-8.55 (m, 1H), 8.56-8.63 (m, 1H), 9.21 (br s, 1H).	555.2
2529		(DMSO-d6) δ 0.31 (br d, 2H, J = 4.0 Hz), 0.51 (br d, 2H, J = 7.3 Hz), 1.04-1.16 (m, 1H), 1.14-1.24 (m, 3H), 1.37-1.44 (m, 2H), 1.92-2.01 (m, 1H), 2.18-2.34 (m, 2H), 3.07 (s, 3H), 3.29-3.40 (m, 4H), 3.71 (app t, 1H, J = 4.7 Hz), 3.80 (app t, 1H, J = 5.8 Hz), 4.29-4.40 (app quint, 1H, J = 7.1 Hz), 8.47-8.52 (m, 1H), 8.56-8.63 (m, 1H), 9.17 (br s, 1H).	483.2

TABLE IID-continued

Compd #	Structure	1H NMR data	MS (M + H)+
2530		(DMSO-d6) δ 0.85-0.95 (m, 1H), 1.13-1.20 (m, 2H), 1.43 (br s, 2H), 1.51 (d, 3H, J = 6.8 Hz), 1.67-1.78 (m, 1H), 1.84-1.94 (m, 1H), 2.18-2.24 (m, 1H), 3.07 (s, 3H), 3.24-3.30 (m, 1H), 3.30-3.37 (m, 1H), 3.66-3.80 (m, 2H), 4.22-4.32 (app quint, 1H), 5.08-5.18 (app quint, 1H), 7.35 (app d, 2H, J = 8.2 Hz), 7.55 (app d, 2H, J = 8.6 Hz), 8.50-8.56 (m, 1H), 8.61 (app d, 1H, J = 6.3 Hz), 8.88-9.07 (m, 1H).	618.2

In other embodiments, the compounds of the invention have a structural formula as depicted in Tables IIIA, IIIB, IIIC, IIID, IIIE, and IIIF below and include tautomers, and pharmaceutically acceptable salts, esters, prodrugs, isomers, and solvates of such compounds and such tautomers. The compounds shown in these tables were made according to the methods described herein or analogous thereto.

HCV Replicon assay data for compounds of the invention shown in Table IIIA that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIIA as a falling within the following range: "A"—less than or equal to about 0.5 μM

TABLE IIIA

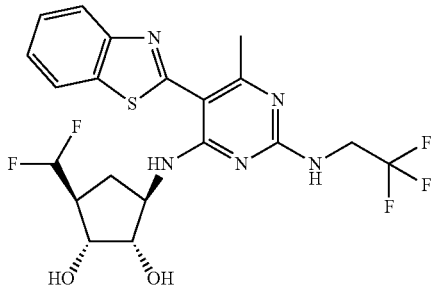
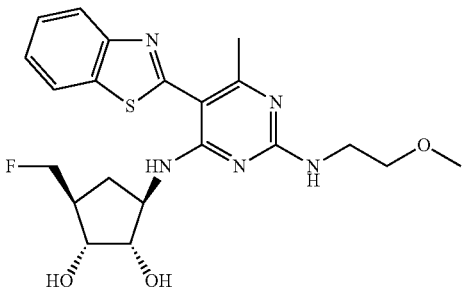
Compd #	Structure	LC-MS or MS (M + H)+
3001		490.3
3006		448.2

TABLE IIIA-continued

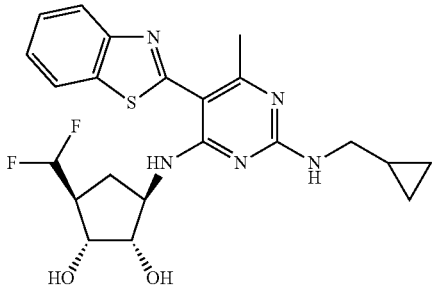
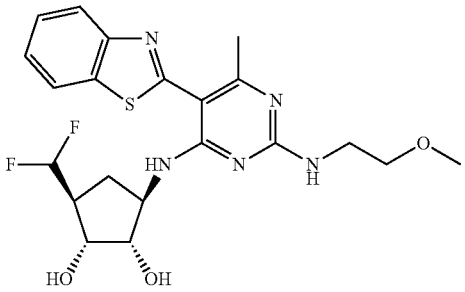
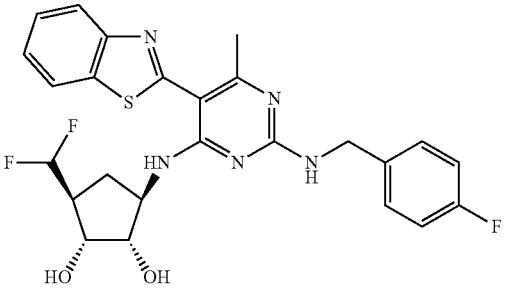
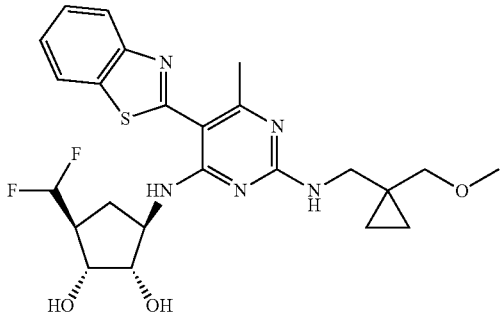
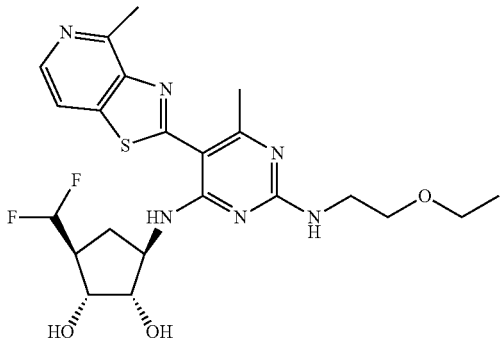
Compd #	Structure	LC-MS or MS $(M + H)^+$
3007		462.3
3011		466.3
3013		516.3
3016		506.3
3017		495.3

TABLE IIIA-continued

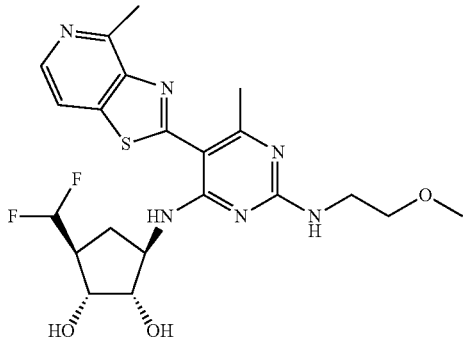
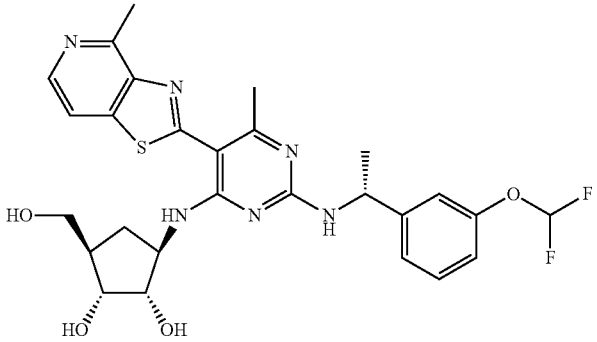
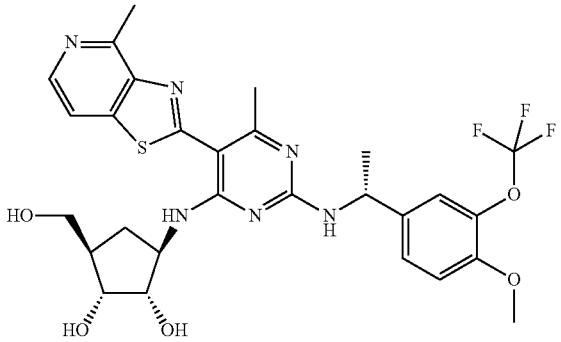
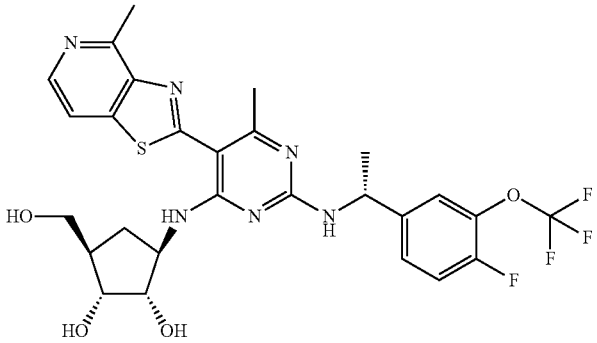
Compd #	Structure	LC-MS or MS $(M + H)^+$
3018		481.3
3019		573.3
3020		621.3
3021		609.3

TABLE IIIA-continued

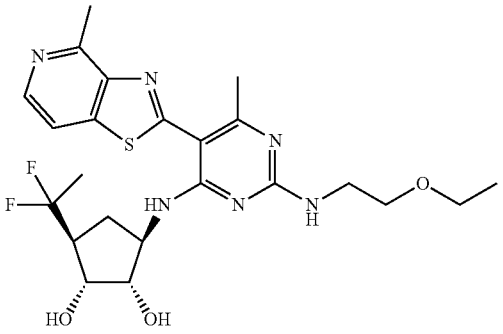
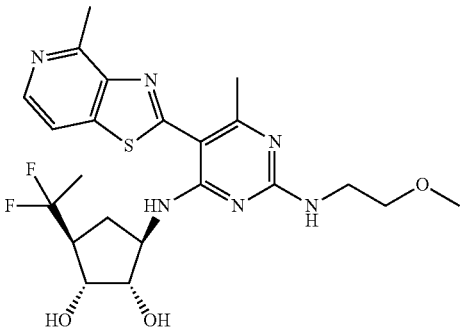
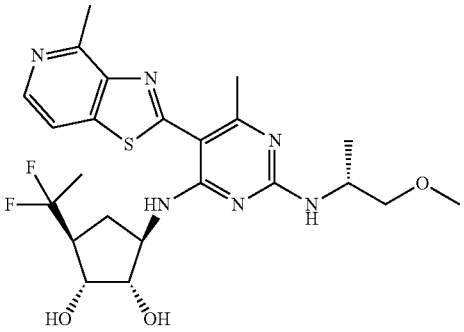
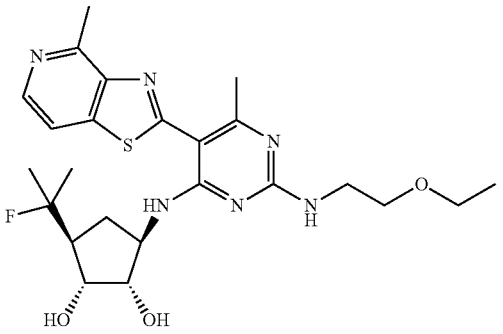
Compd #	Structure	LC-MS or MS $(M + H)^+$
3022		509.3
3023		495.3
3024		509.2
3025		505.3

TABLE IIIA-continued

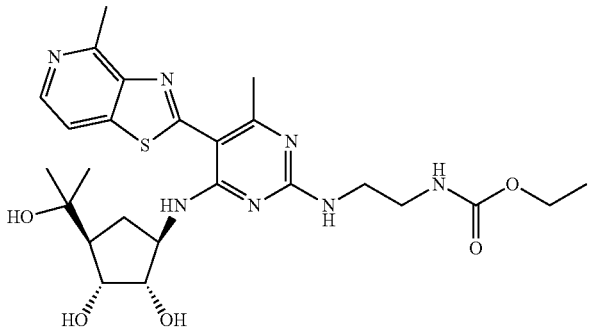
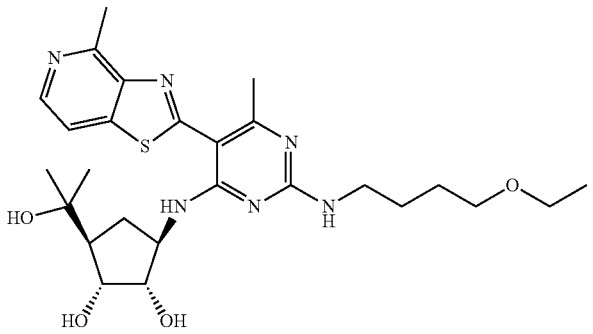
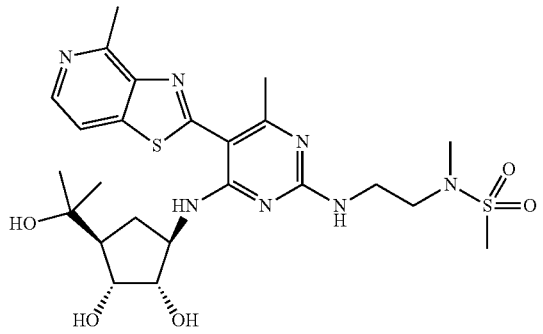
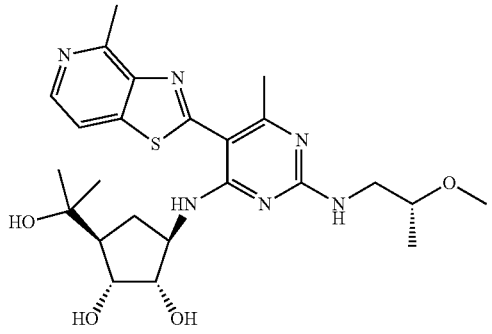
Compd #	Structure	LC-MS or MS $(M + H)^+$
3026		546.3
3028		531.3
3029		566.3
3030		503.3

TABLE IIIA-continued

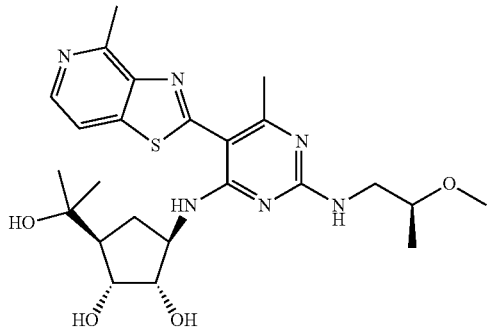
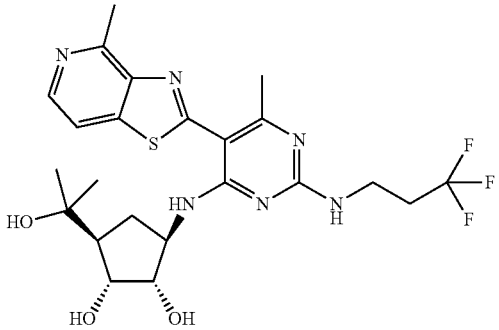
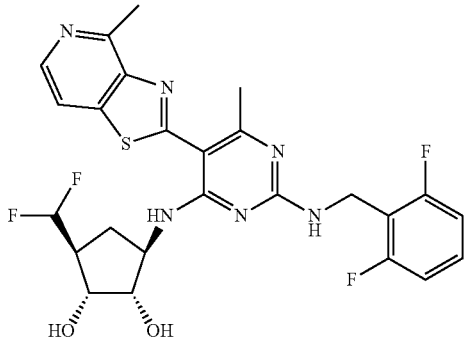
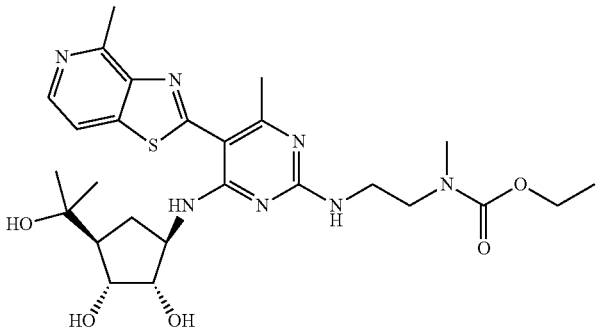
Compd #	Structure	LC-MS or MS $(M + H)^+$
3031		503.3
3032		527.3
3033		549.3
3034		560.3

TABLE IIIA-continued

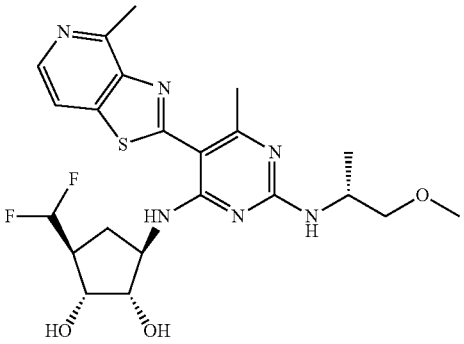
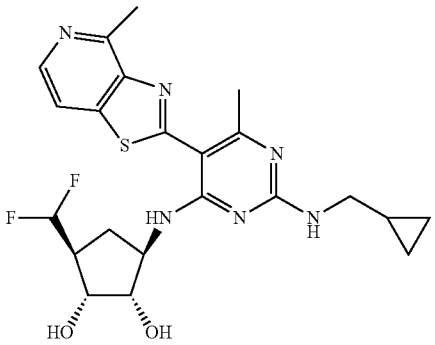
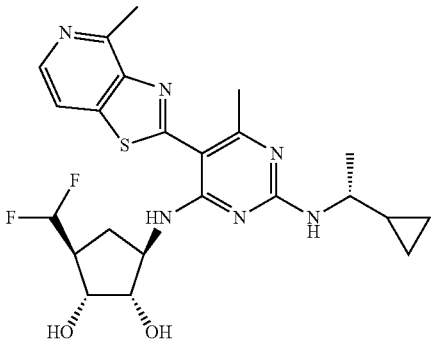
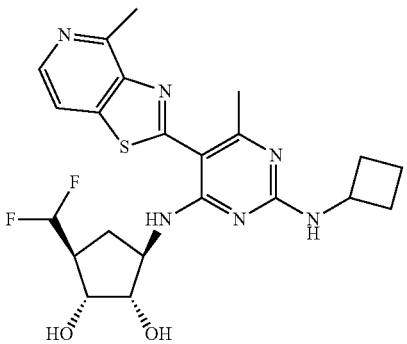
Compd #	Structure	LC-MS or MS $(M + H)^+$
3035		495.3
3036		477.3
3037		491.3
3038		477.3

TABLE IIIA-continued

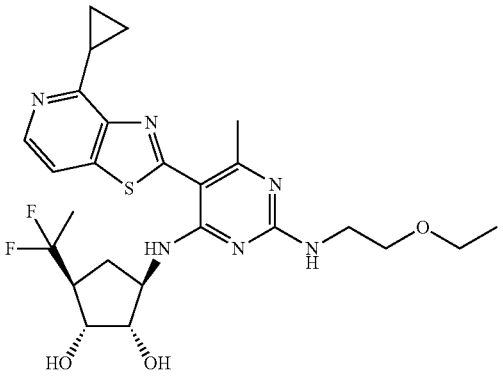
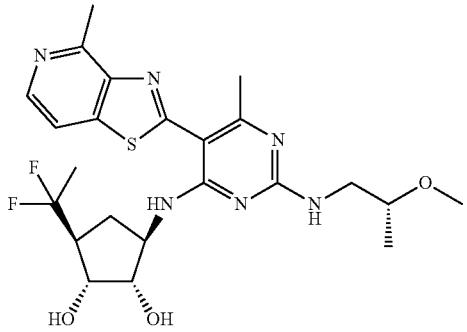
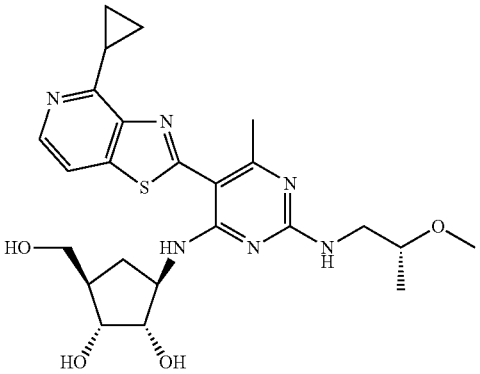
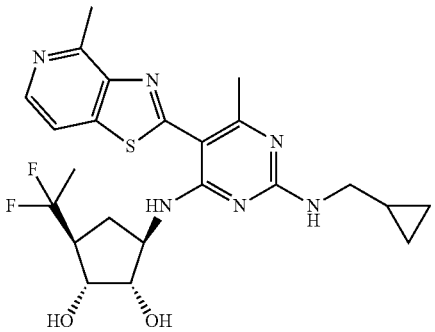
Compd #	Structure	LC-MS or MS $(M + H)^+$
3039		535.3
3040		509.3
3041		501.3
3042		491.3

TABLE IIIA-continued

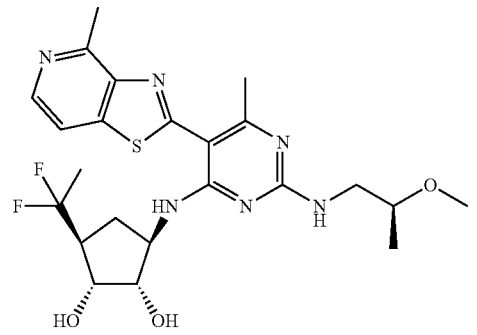
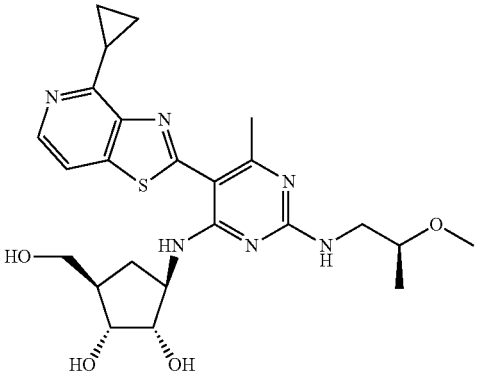
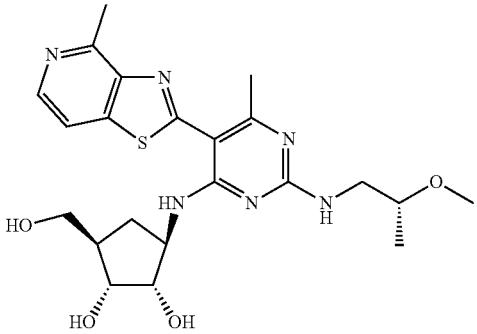
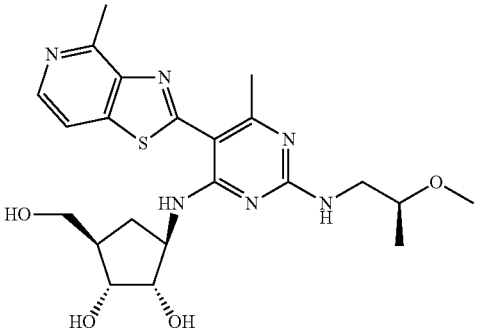
Compd #	Structure	LC-MS or MS $(M + H)^+$
3043		509.3
3044		501.3
3045		475.3
3046		475.3

TABLE IIIA-continued

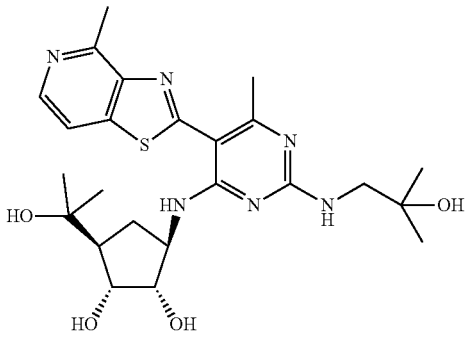
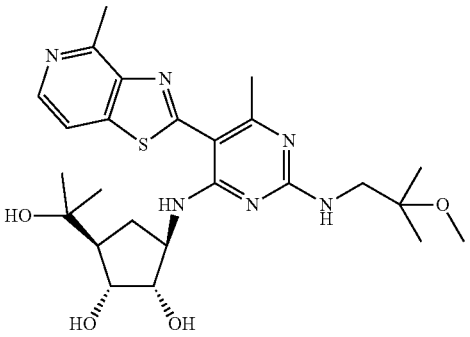
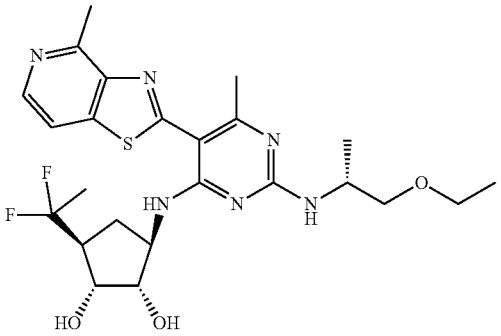
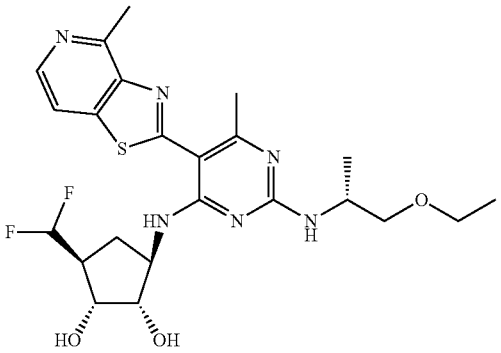
Compd #	Structure	LC-MS or MS $(M + H)^+$
3047		503.3
3048		517.3
3049		523.3
3050		509.3

TABLE IIIA-continued

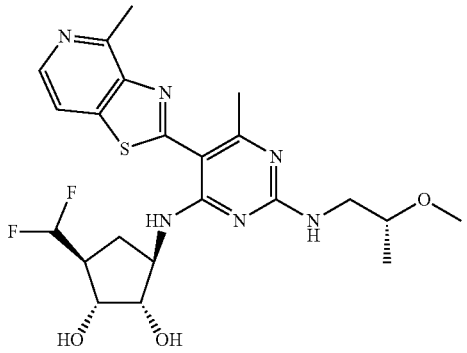
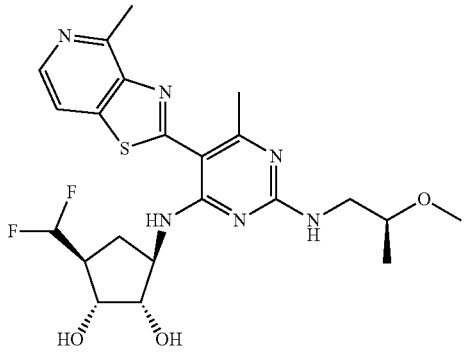
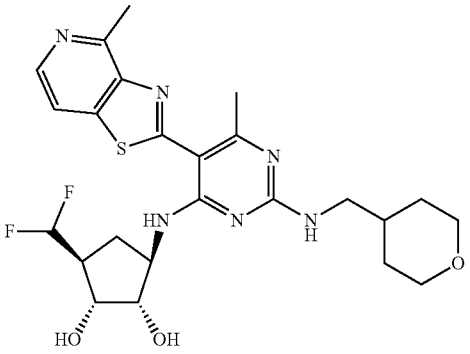
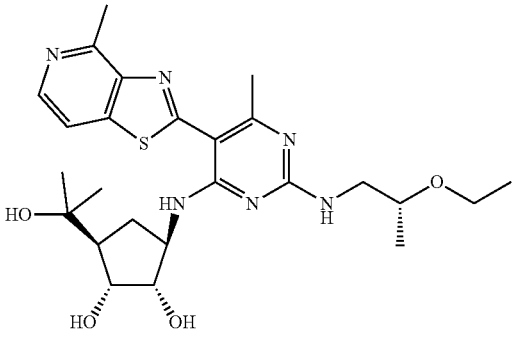
Compd #	Structure	LC-MS or MS $(M + H)^+$
3051		495.3
3052		495.3
3053		521.3
3054		517.3

TABLE IIIA-continued

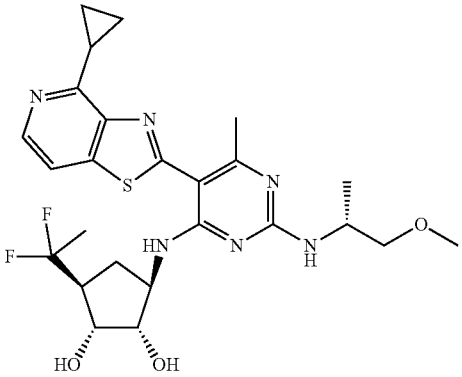
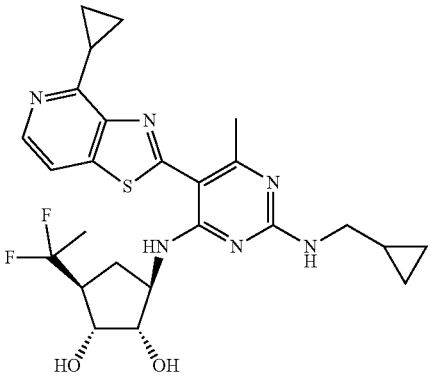
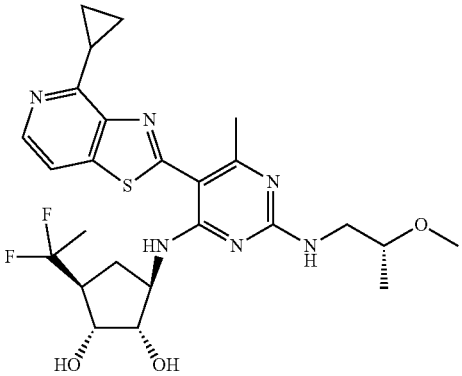
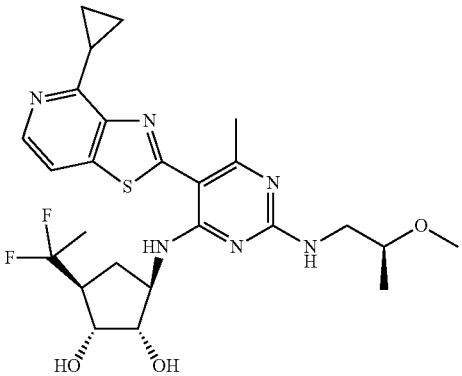
Compd #	Structure	LC-MS or MS $(M + H)^+$
3055		535.3
3056		517.3
3057		535.3
3058		535.3

TABLE IIIA-continued

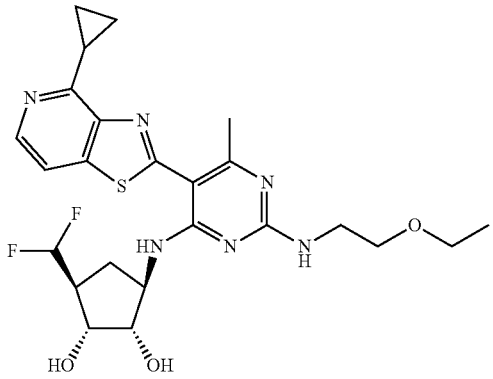
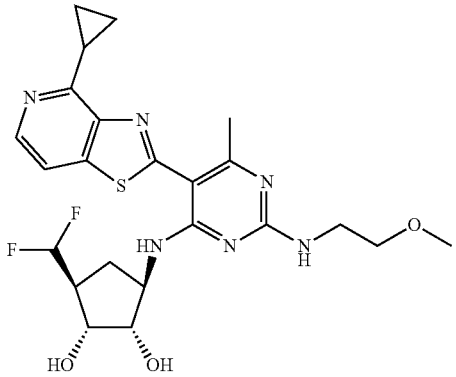
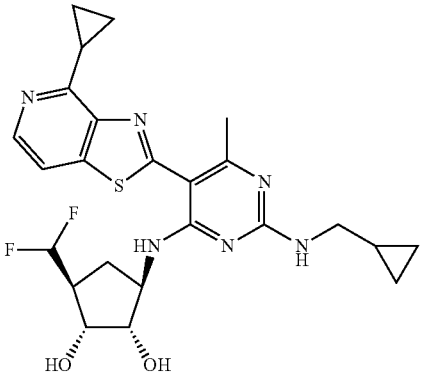
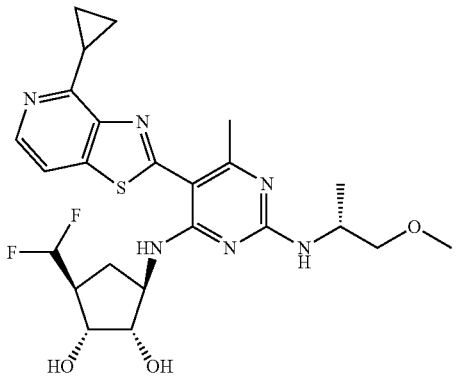
Compd #	Structure	LC-MS or MS $(M + H)^+$
3059		521.3
3060		507.3
3061		503.3
3062		521.3

TABLE IIIA-continued

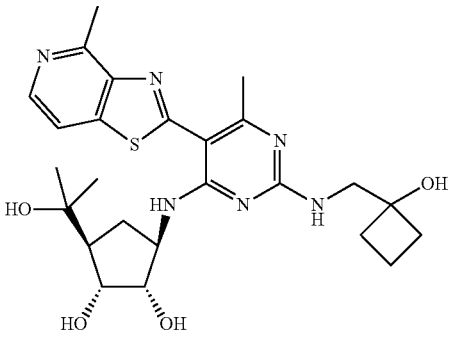
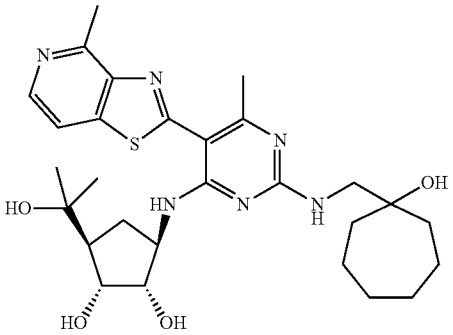
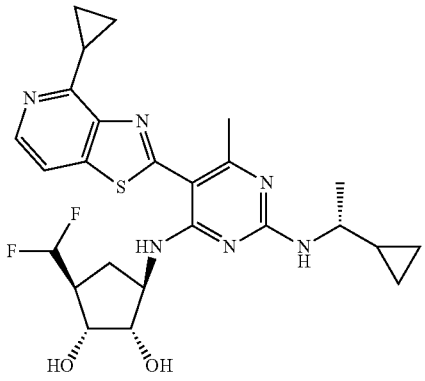
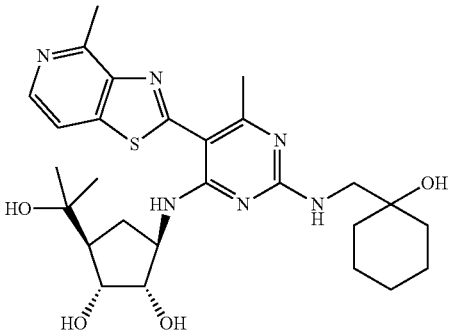
Compd #	Structure	LC-MS or MS $(M + H)^+$
3063		515.3
3064		557.3
3065		517.3
3066		543.3

TABLE IIIA-continued

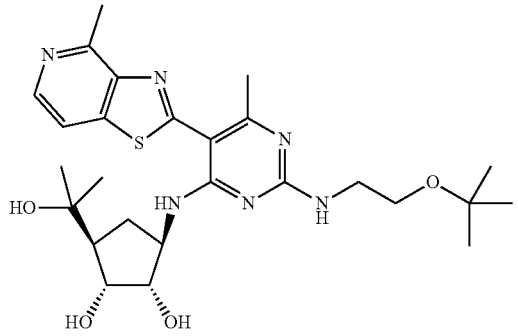
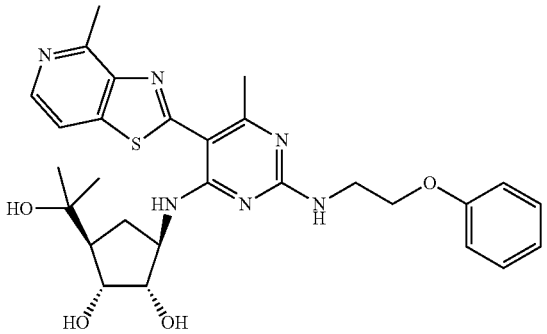
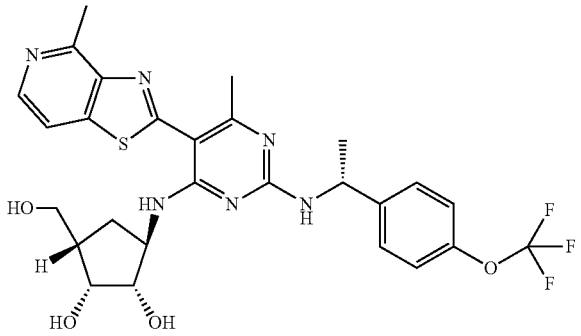
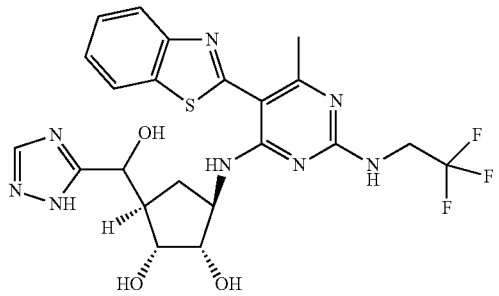
Compd #	Structure	LC-MS or MS $(M + H)^+$
3067		531.3
3068		551.3
3104		591.2
3105		537.2

TABLE IIIA-continued

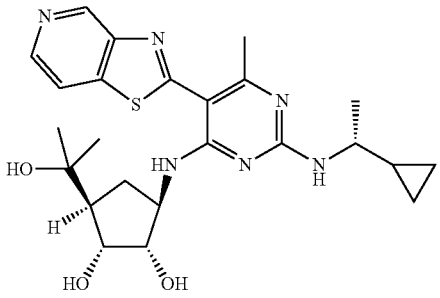
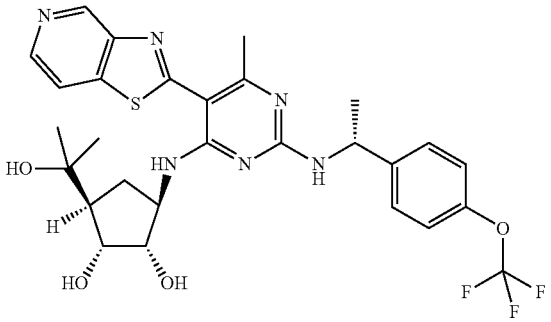
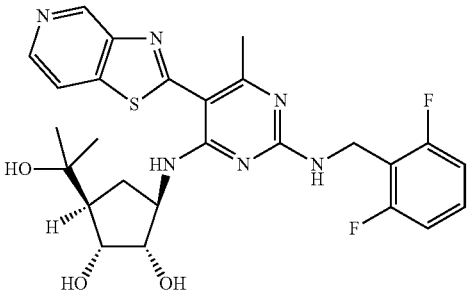
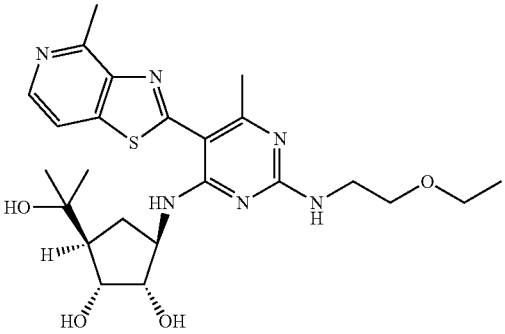
Compd #	Structure	LC-MS or MS $(M + H)^+$
3106		485.2
3107		605.2
3108		543.2
3109		503.2

TABLE IIIA-continued

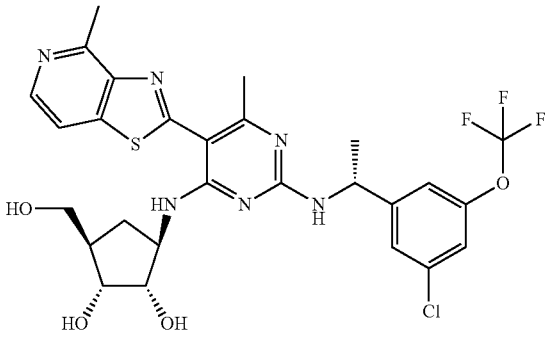
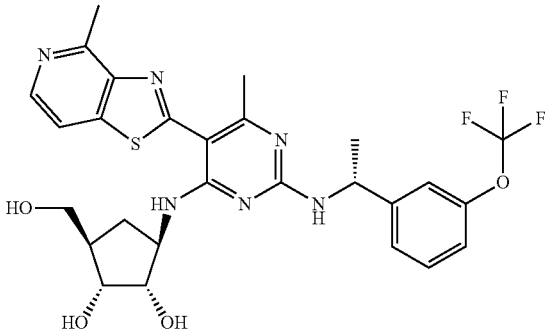
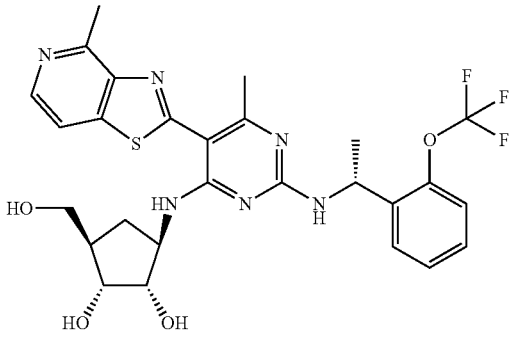
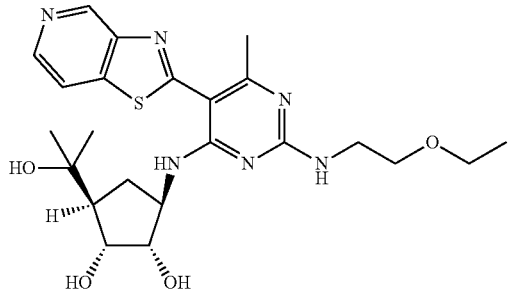
Compd #	Structure	LC-MS or MS $(M + H)^+$
3111		626.2
3112		591.2
3113		591.2
3114		489.2

TABLE IIIA-continued

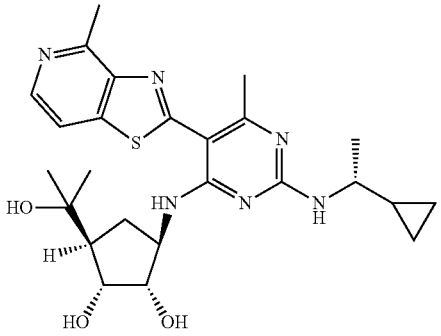
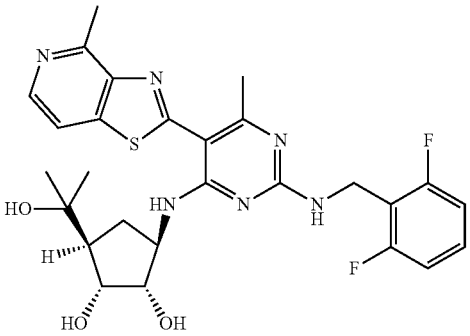
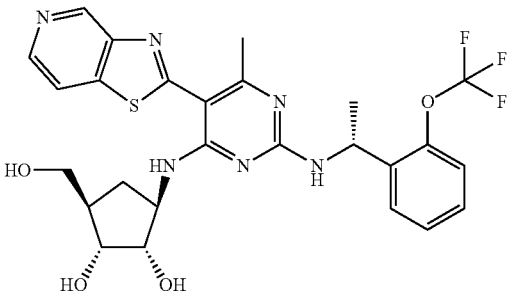
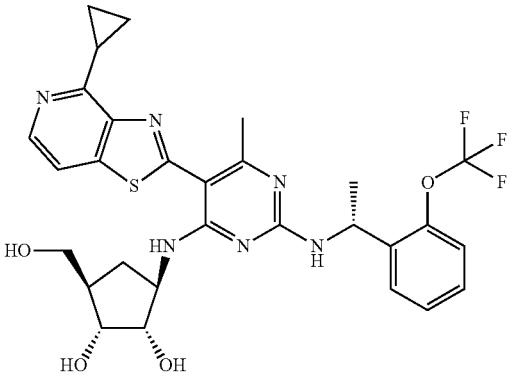
Compd #	Structure	LC-MS or MS $(M + H)^+$
3115		499.2
3116		557.2
3117		577.2
3118		617.2

TABLE IIIA-continued

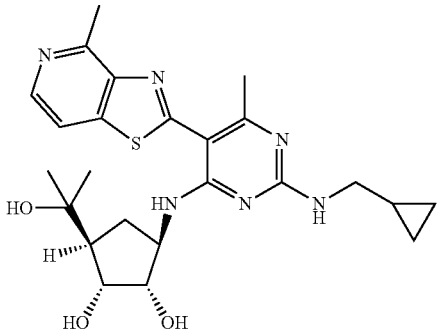
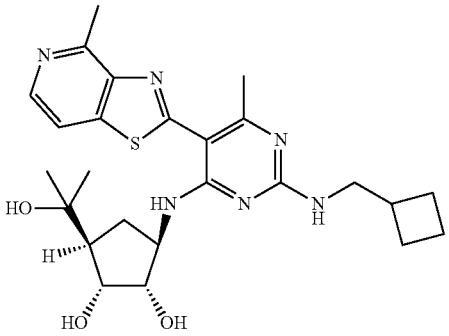
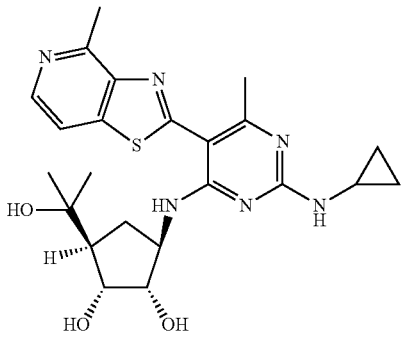
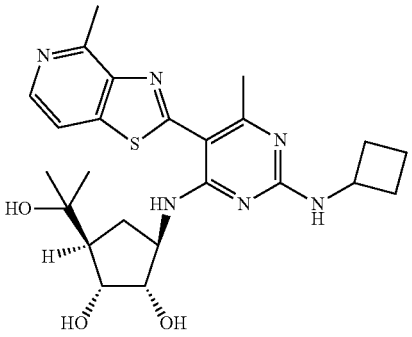
Compd #	Structure	LC-MS or MS $(M + H)^+$
3119		485.2
3120		499.2
3121		471.2
3122		485.2

TABLE IIIA-continued

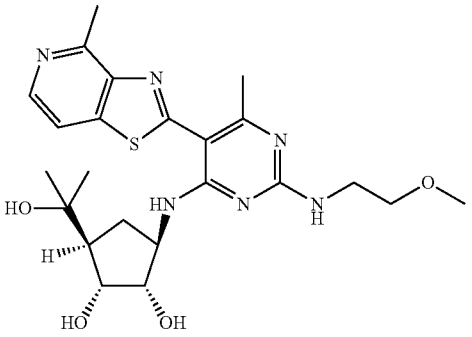
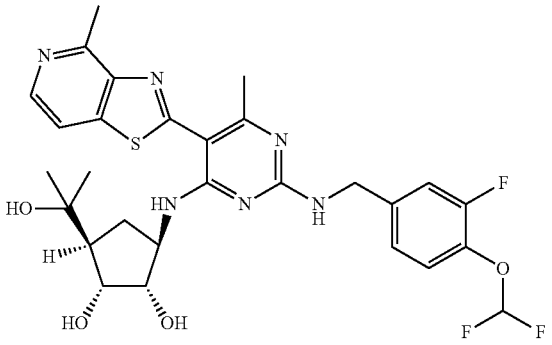
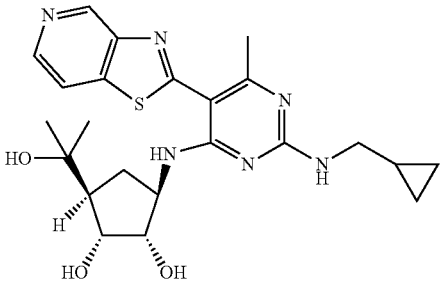
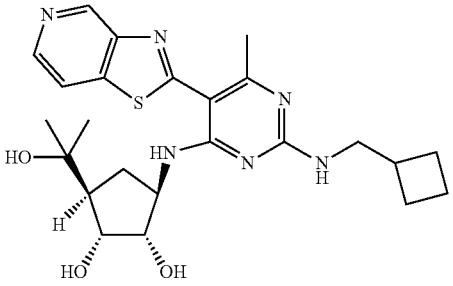
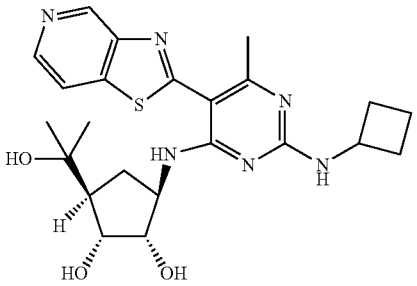
Compd #	Structure	LC-MS or MS $(M + H)^+$
3123		489.2
3125		605.2
3126		471.2
3127		485.2
3129		471.2

TABLE IIIA-continued

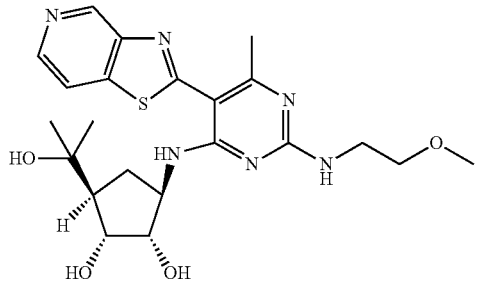
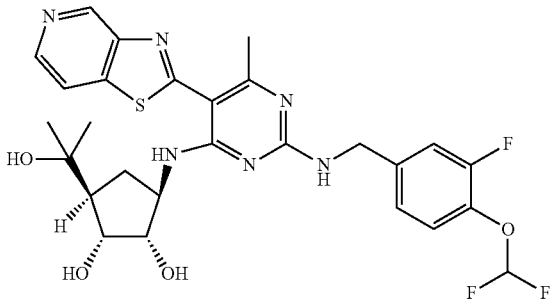
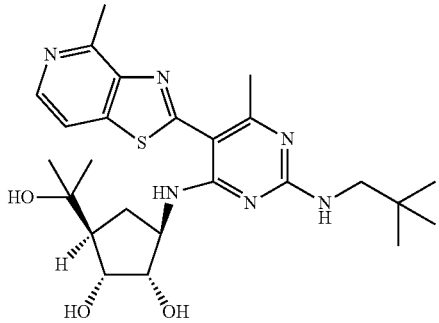
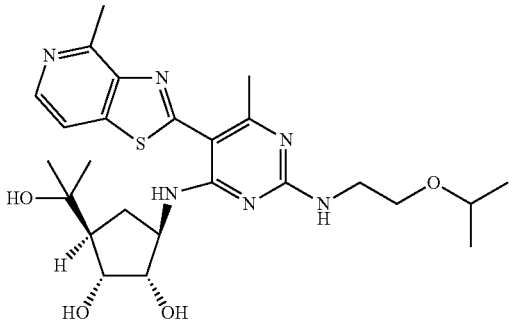
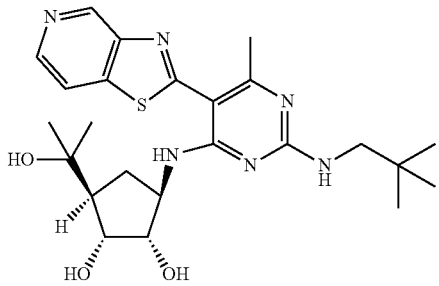
Compd #	Structure	LC-MS or MS $(M + H)^+$
3130		475.2
3132		591.2
3133		501.2
3135		517.2
3136		487.2

TABLE IIIA-continued

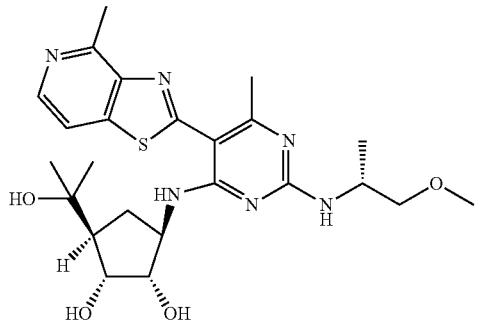
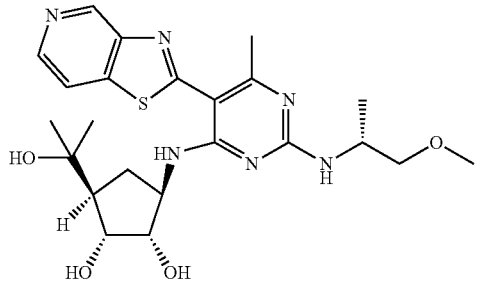
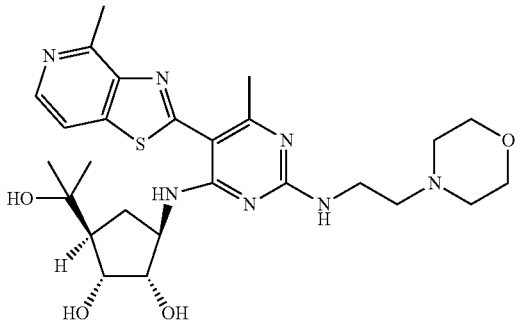
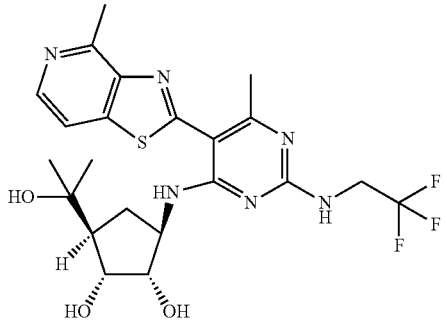
Compd #	Structure	LC-MS or MS $(M + H)^+$
3137		503.2
3138		489.2
3139		544.2
3141		513.2

TABLE IIIA-continued

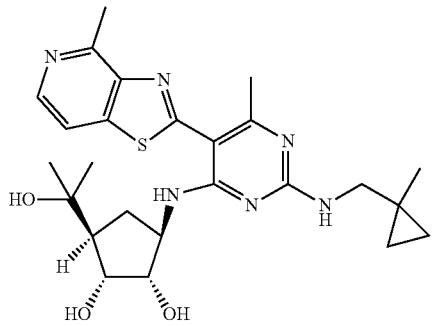
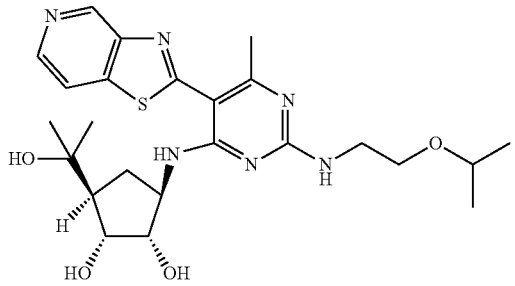
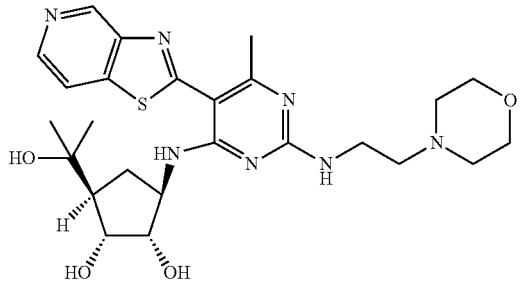
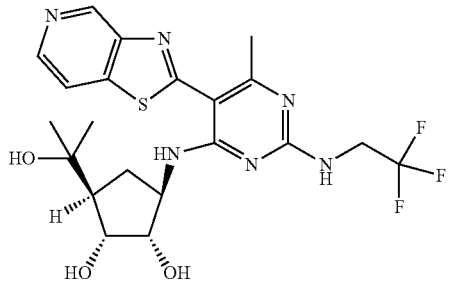
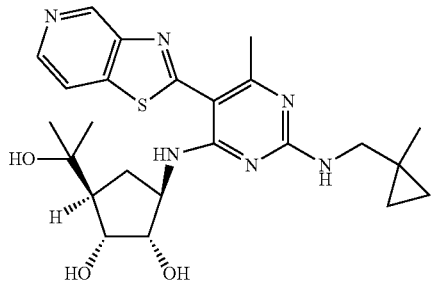
Compd #	Structure	LC-MS or MS $(M + H)^+$
3142		499.2
3144		503.2
3145		530.2
3146		499.2
3147		485.2

TABLE IIIA-continued

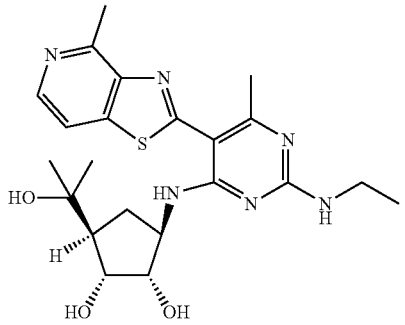
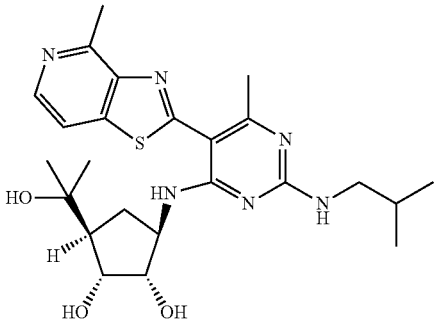
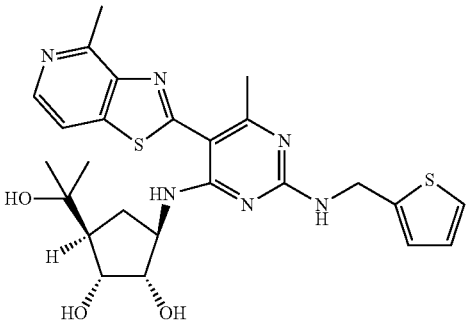
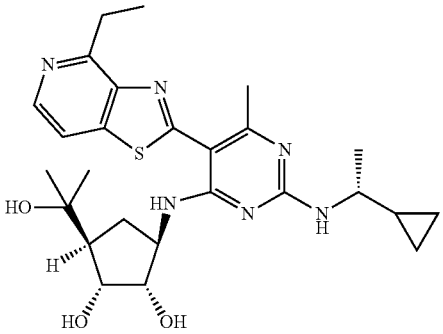
Compd #	Structure	LC-MS or MS $(M + H)^+$
3148		459.2
3149		487.2
3153		527.2
3154		513.2

TABLE IIIA-continued

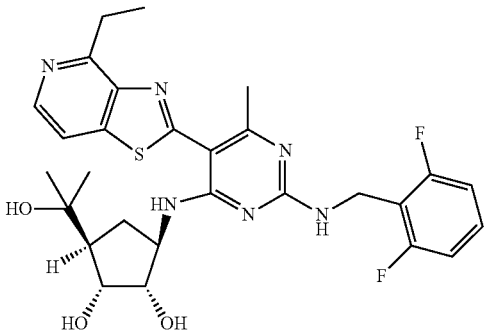
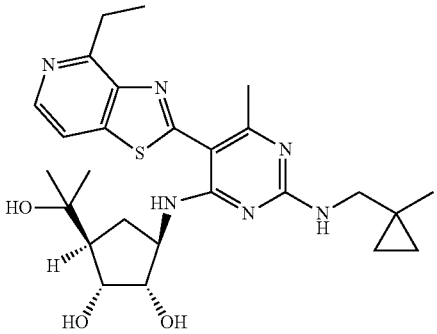
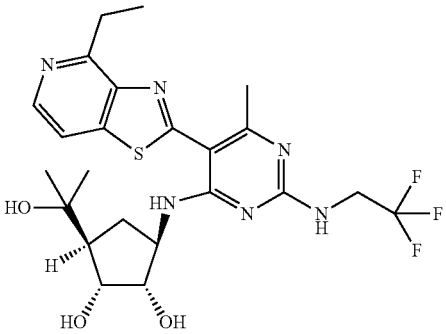
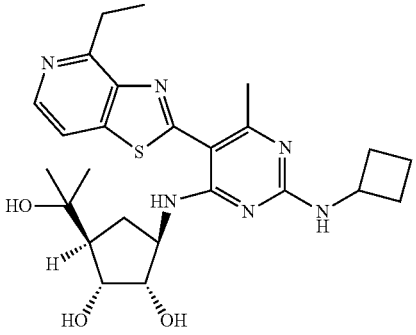
Compd #	Structure	LC-MS or MS $(M + H)^+$
3155		571.2
3156		513.2
3157		527.2
3158		499.2

TABLE IIIA-continued

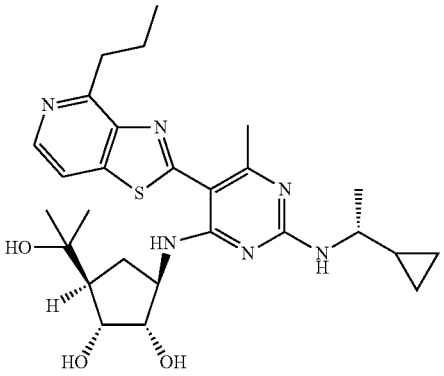
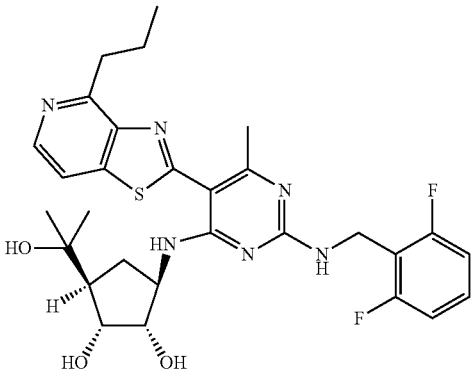
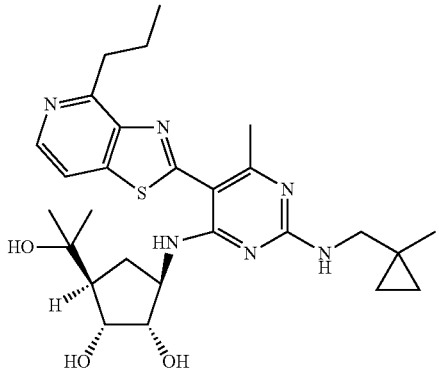
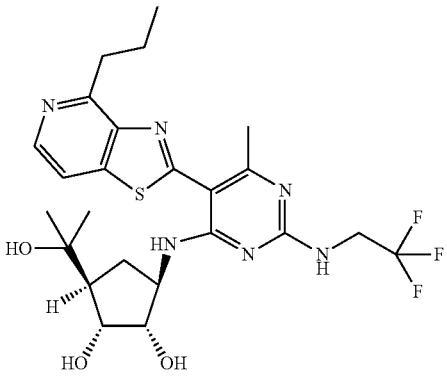
Compd #	Structure	LC-MS or MS $(M + H)^+$
3159		527.2
3160		585.2
3161		527.2
3162		541.2

TABLE IIIA-continued

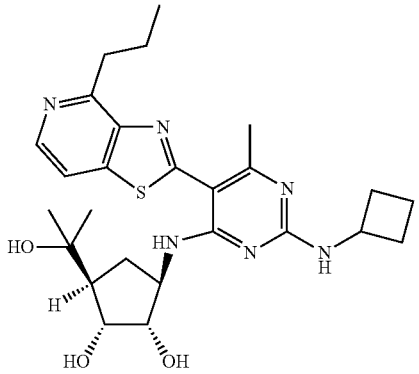
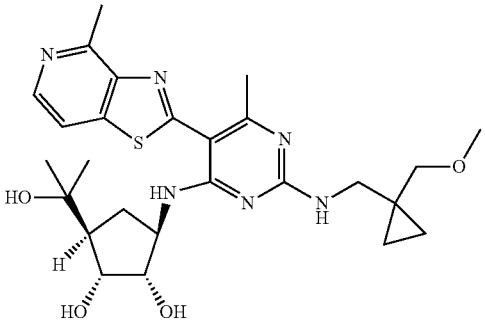
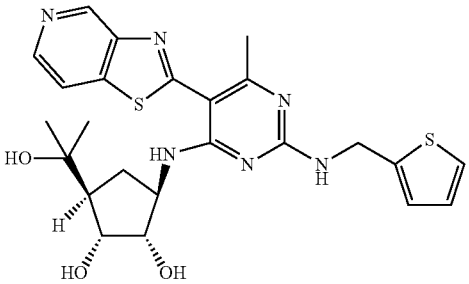
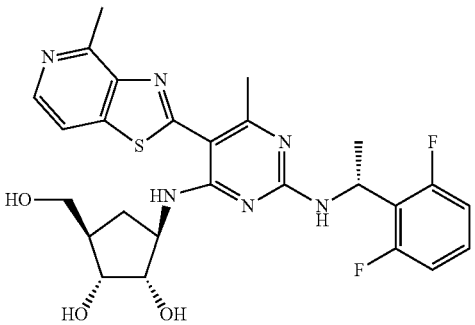
Compd #	Structure	LC-MS or MS $(M + H)^+$
3163		513.2
3164		529.2
3165		513.2
3166		542.2

TABLE IIIA-continued

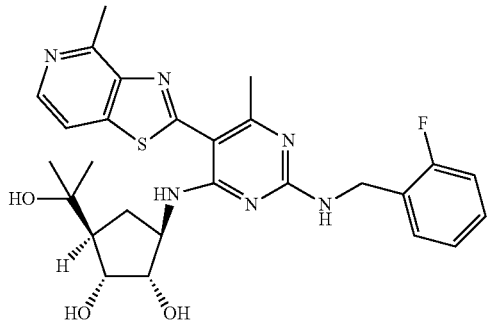
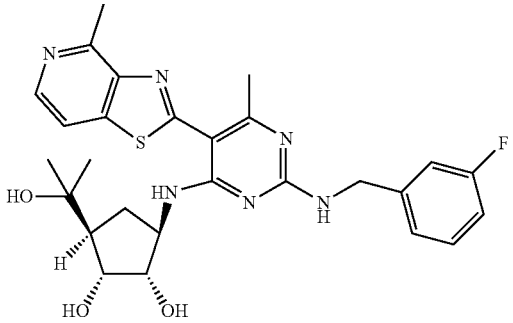
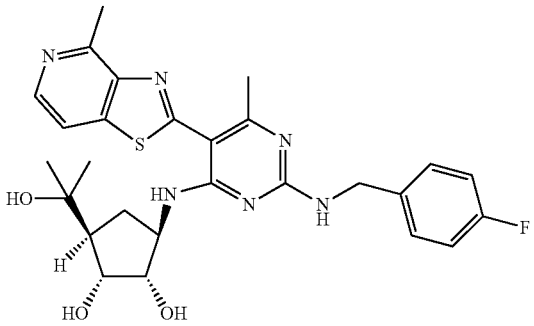
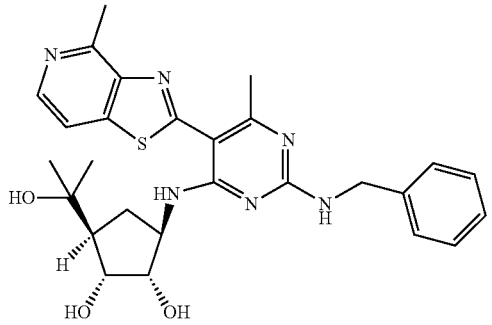
Compd #	Structure	LC-MS or MS $(M + H)^+$
3167		539.2
3168		539.2
3169		539.2
3170		521.2

TABLE IIIA-continued

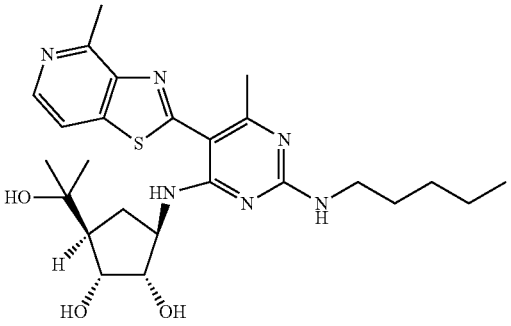
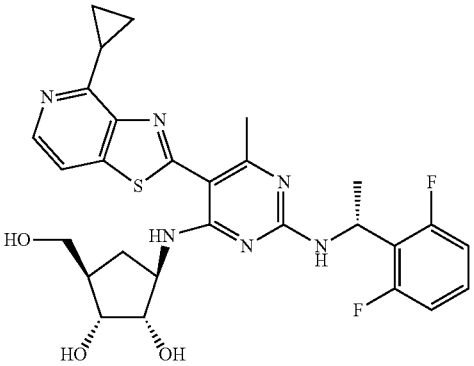
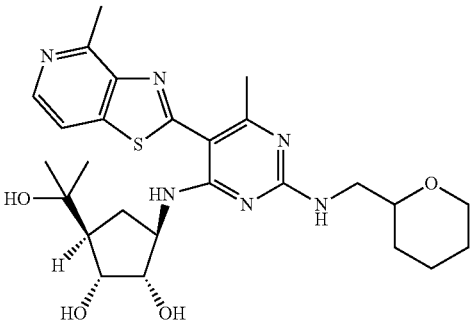
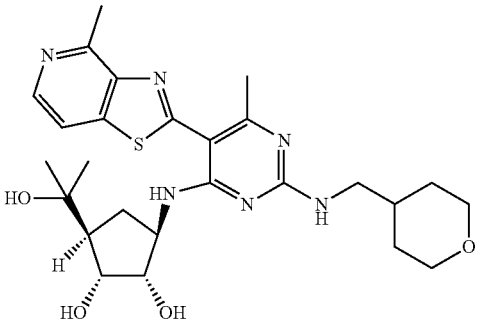
Compd #	Structure	LC-MS or MS $(M + H)^+$
3171		501.2
3174		569.2
3175		529.2
3176		529.2

TABLE IIIA-continued

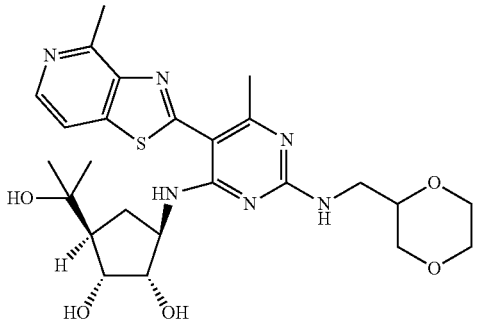
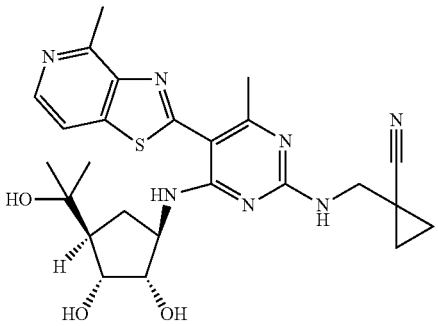
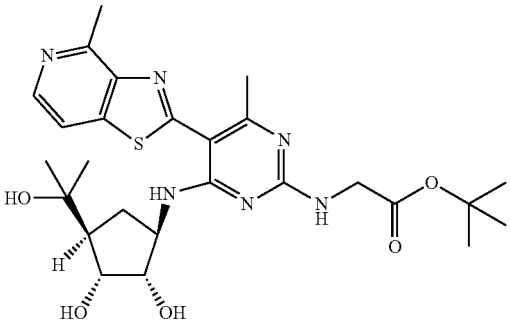
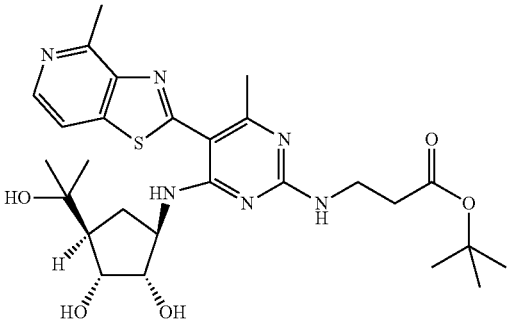
Compd #	Structure	LC-MS or MS $(M + H)^+$
3177		531.2
3178		510.2
3179		545.2
3181		559.2

TABLE IIIA-continued

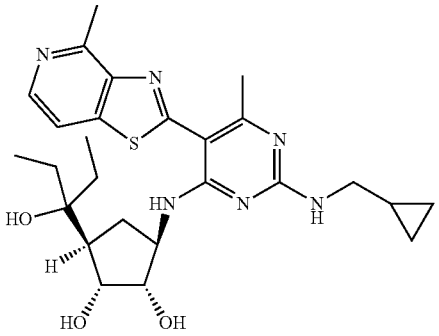
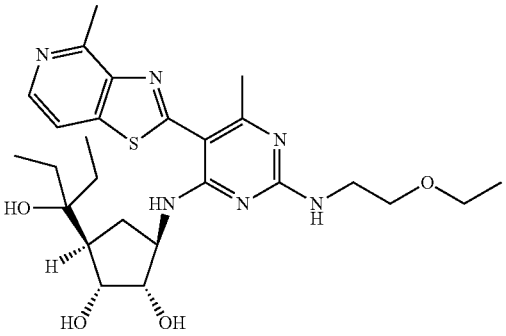
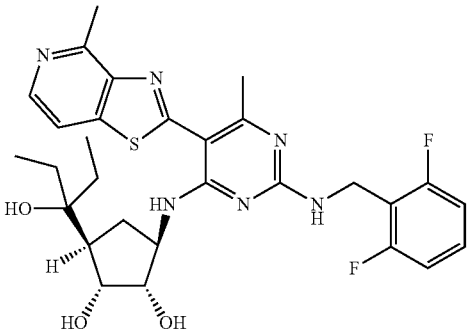
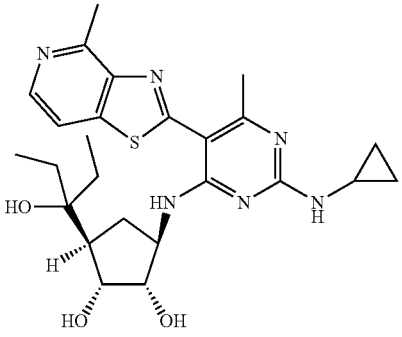
Compd #	Structure	LC-MS or MS $(M + H)^+$
3182		513.2
3183		531.2
3185		585.2
3186		499.2

TABLE IIIA-continued

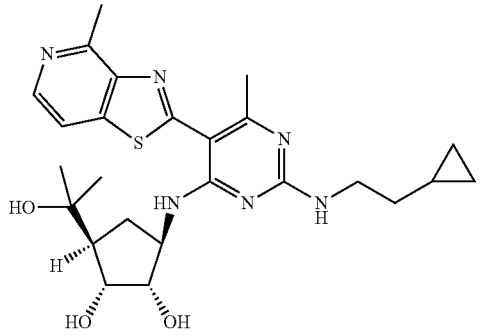
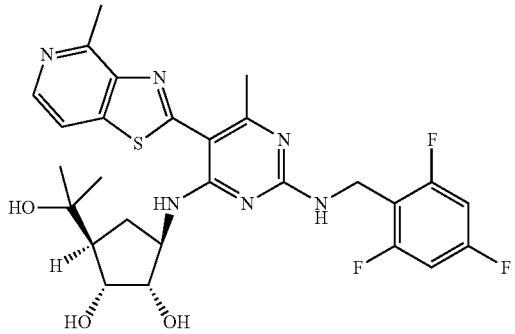
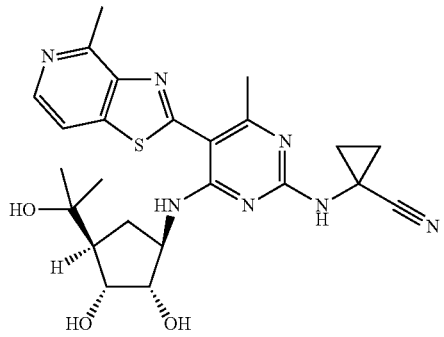
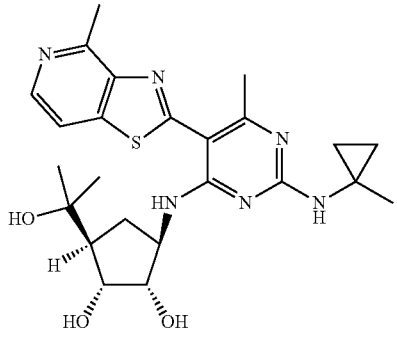
Compd #	Structure	LC-MS or MS $(M + H)^+$
3187		499.2
3188		575.2
3189		496.2
3190		485.2

TABLE IIIA-continued

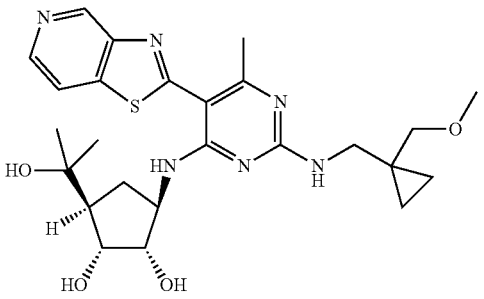
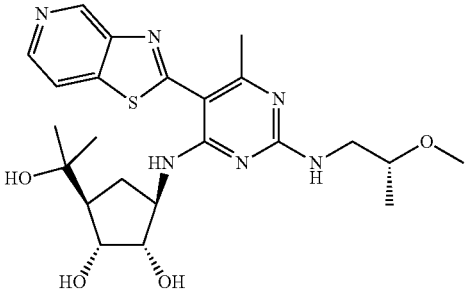
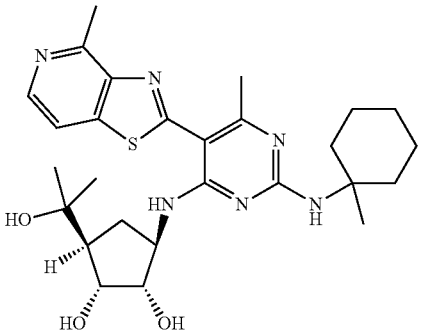
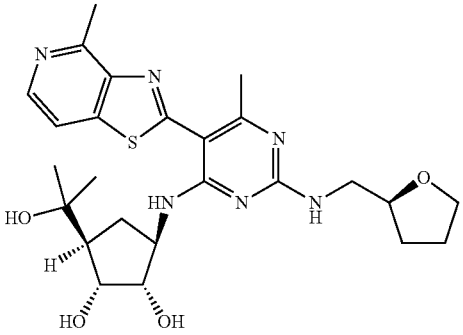
Compd #	Structure	LC-MS or MS $(M + H)^+$
3191		515.2
3192		489.2
3193		527.2
3194		515.2

TABLE IIIA-continued

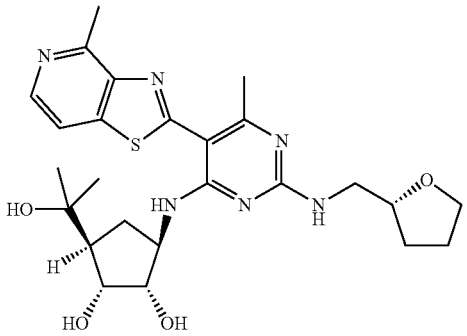
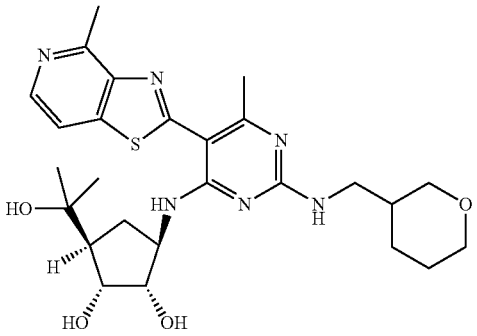
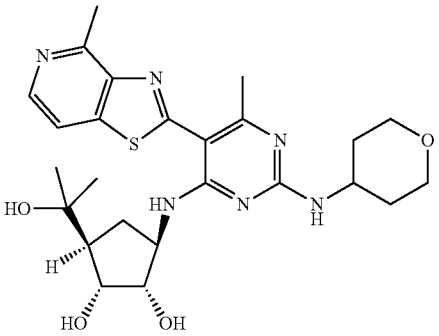
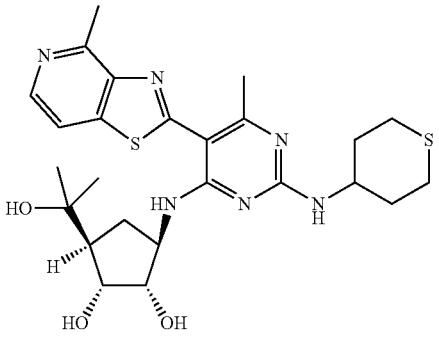
Compd #	Structure	LC-MS or MS $(M + H)^+$
3195		515.2
3197		529.2
3198		515.2
3199		531.2

TABLE IIIA-continued

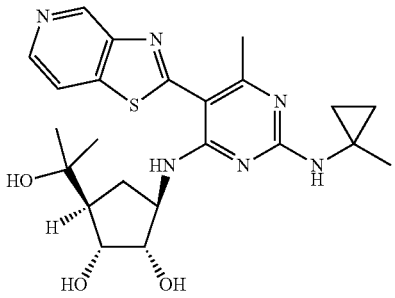
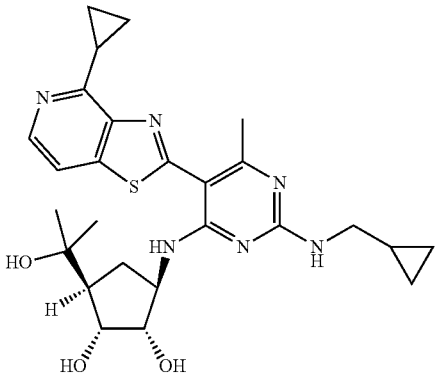
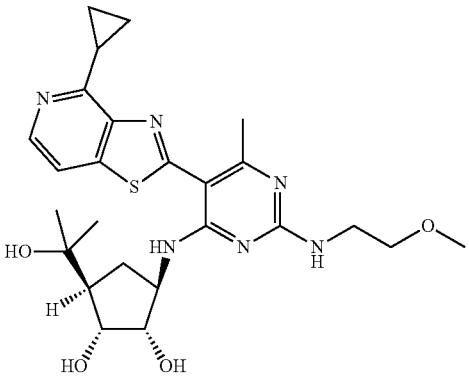
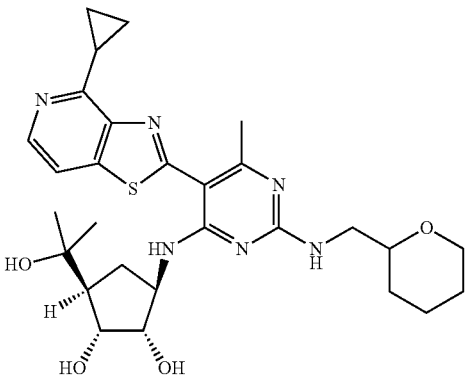
Compd #	Structure	LC-MS or MS $(M + H)^+$
3200		471.2
3201		511.2
3202		515.2
3204		555.2

TABLE IIIA-continued

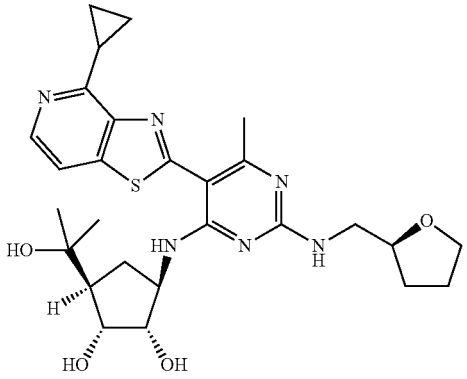
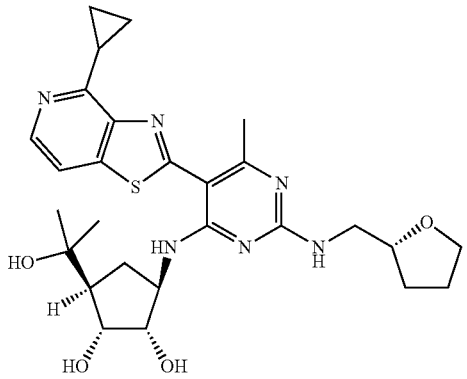
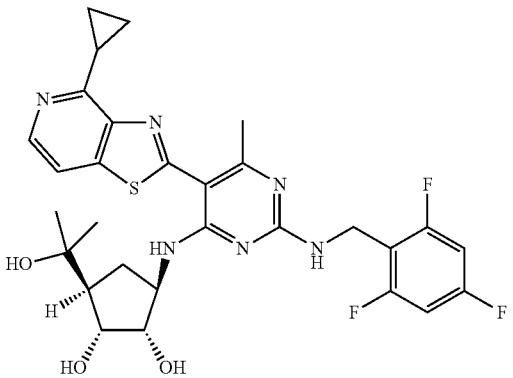
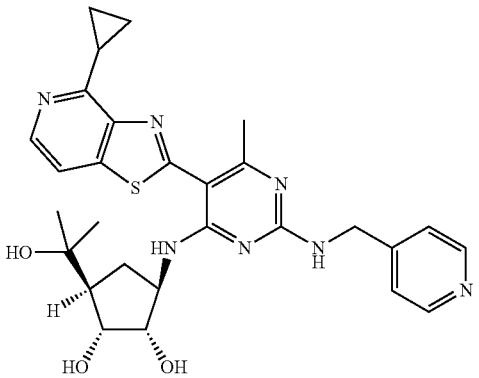
Compd #	Structure	LC-MS or MS $(M + H)^+$
3205		541.2
3206		541.2
3207		601.2
3208		548.2

TABLE IIIA-continued

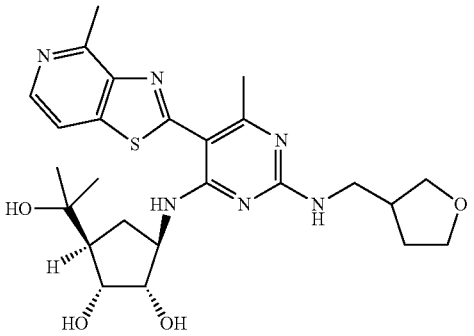
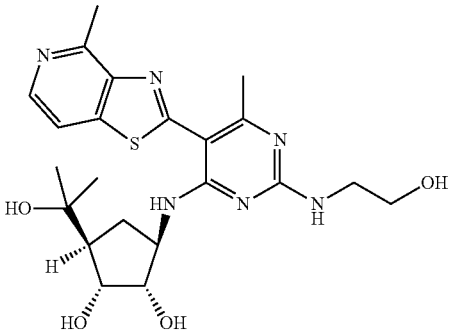
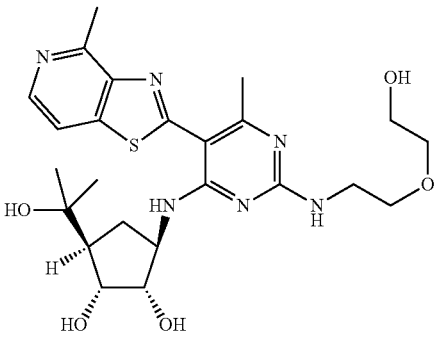
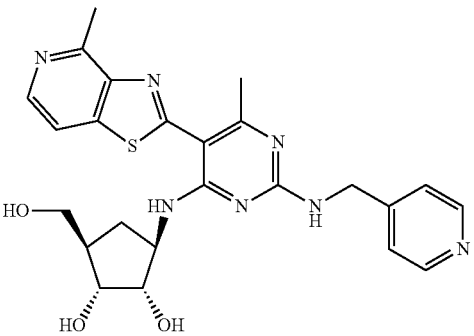
Compd #	Structure	LC-MS or MS $(M + H)^+$
3209		515.2
3210		475.2
3211		519.2
3212		494.2

TABLE IIIA-continued

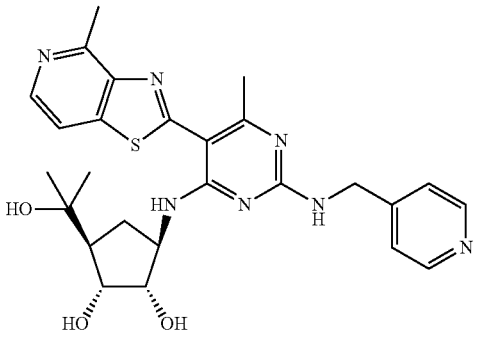
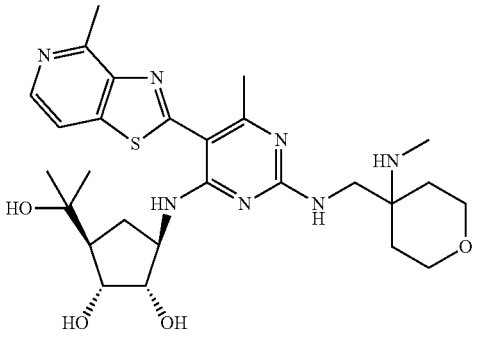
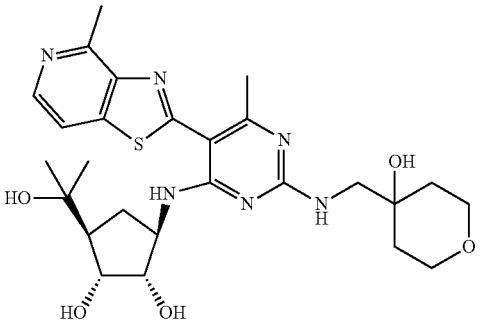
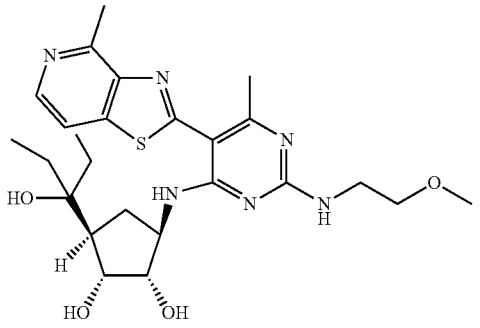
Compd #	Structure	LC-MS or MS $(M + H)^+$
3213		522.2
3214		558.2
3215		545.2
3216		517.2

TABLE IIIA-continued

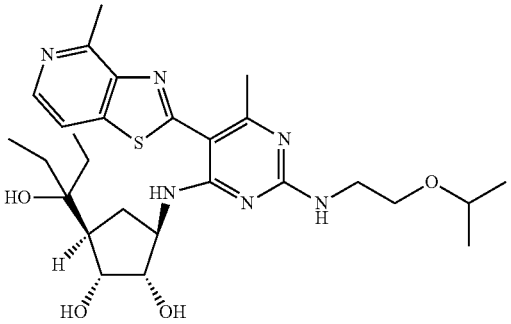
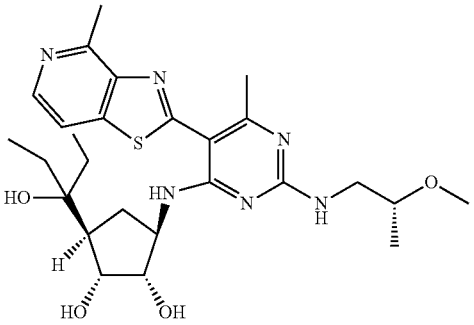
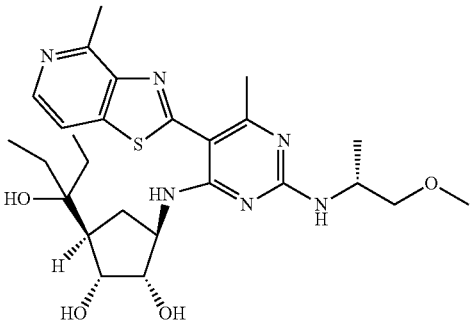
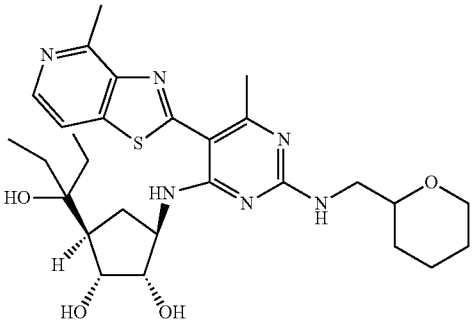
Compd #	Structure	LC-MS or MS $(M + H)^+$
3217		545.2
3218		531.2
3219		531.2
3220		557.2

TABLE IIIA-continued

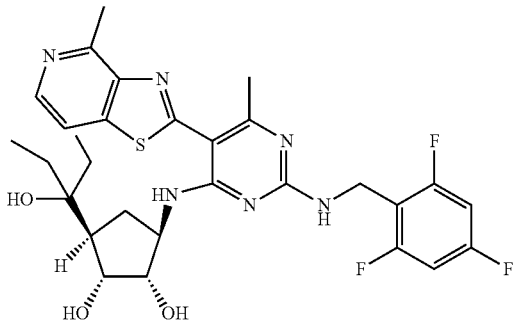
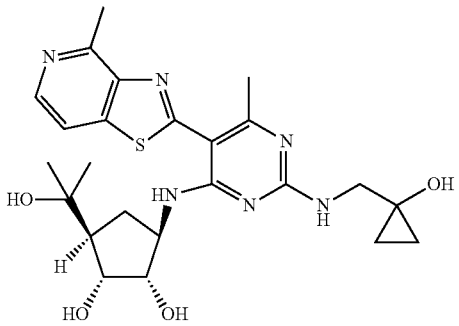
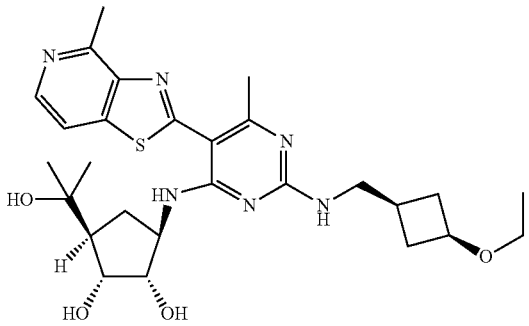
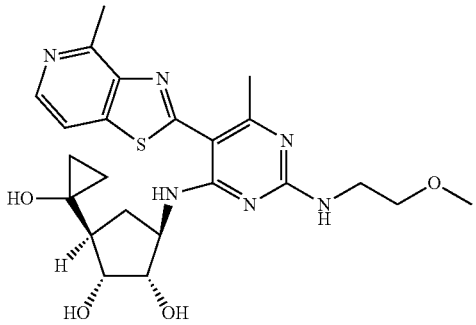
Compd #	Structure	LC-MS or MS $(M + H)^+$
3222		603.2
3224		501.2
3225		543.2
3226		487.2

TABLE IIIA-continued

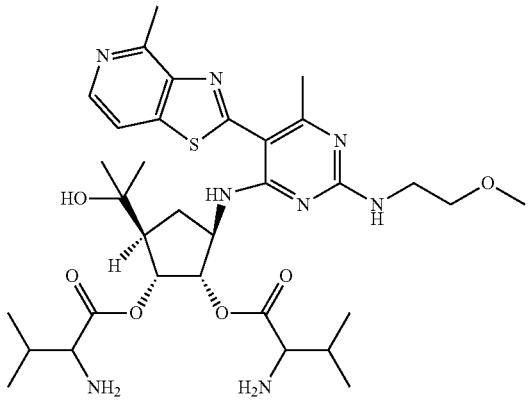
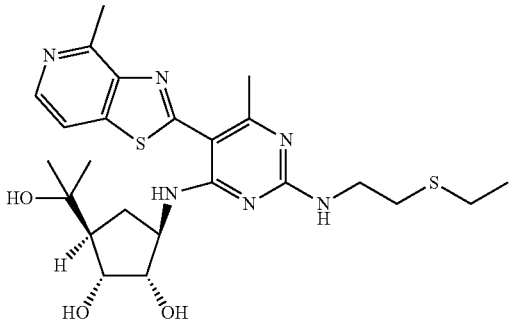
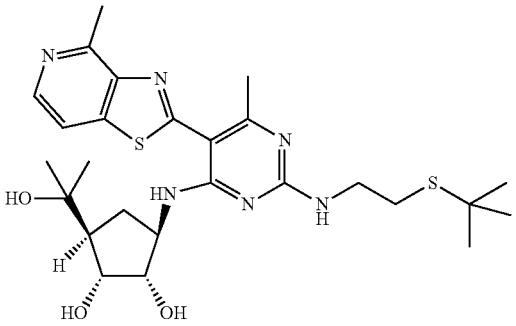
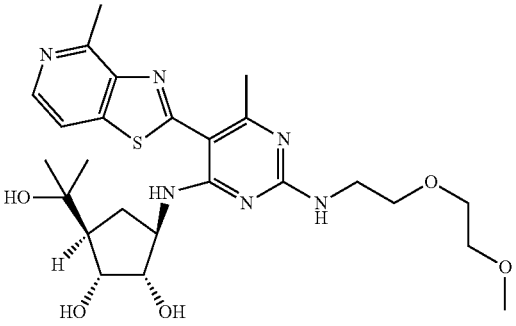
Compd #	Structure	LC-MS or MS $(M + H)^+$
3227		687.2
3229		519.2
3230		547.2
3231		533.2

TABLE IIIA-continued

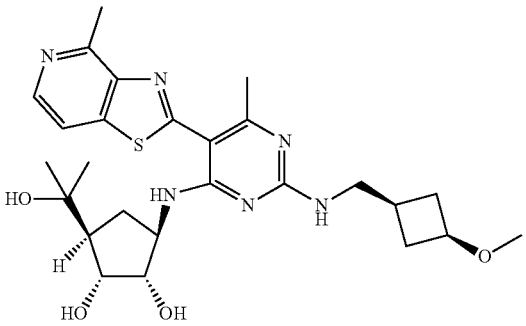
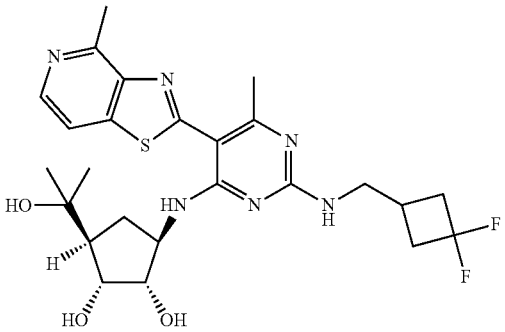
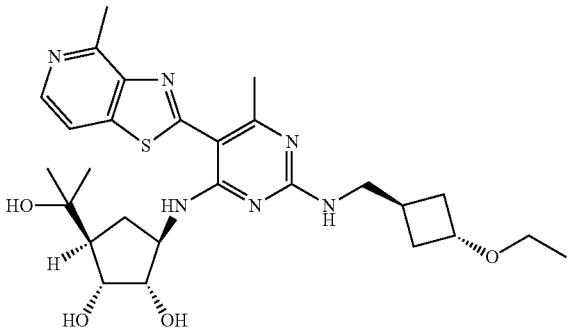
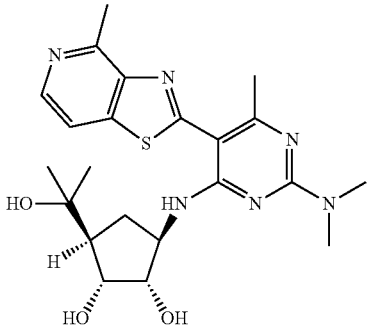
Compd #	Structure	LC-MS or MS $(M + H)^+$
3233		529.2
3239		535.2
3240		543.2
3241		459.2

TABLE IIIA-continued

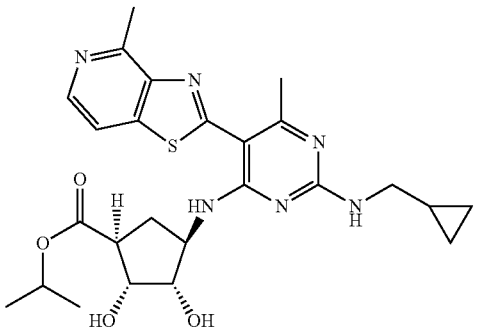
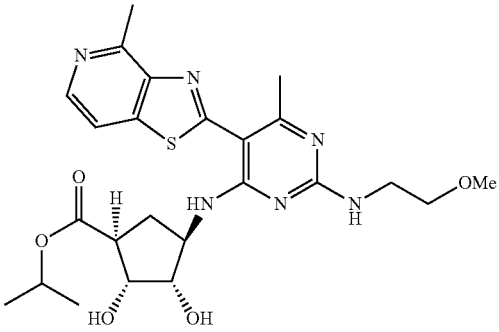
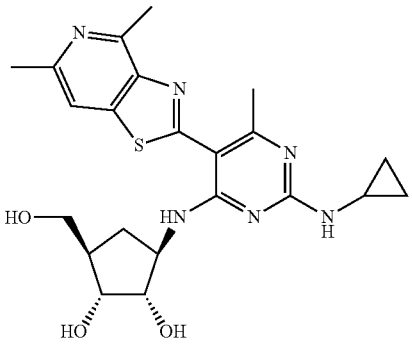
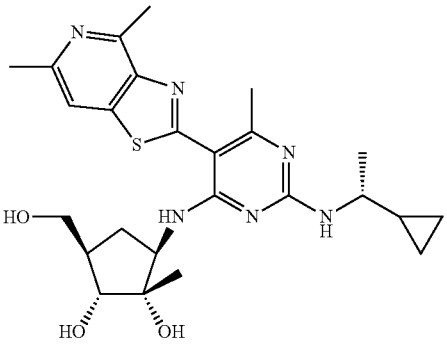
Compd #	Structure	LC-MS or MS $(M + H)^+$
3242		513.2
3243		517.2
3301		457.3
3302		499.2

TABLE IIIA-continued

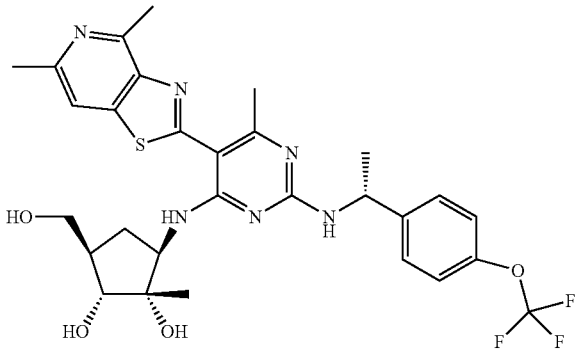
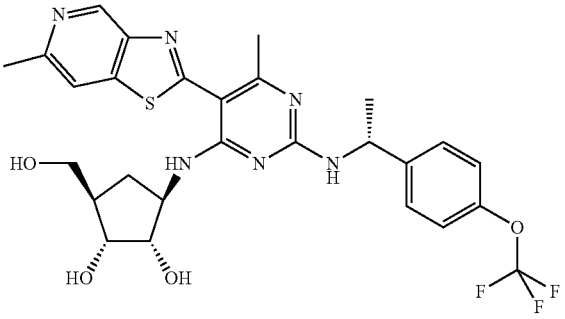
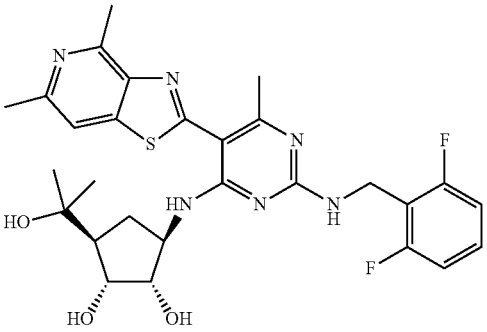
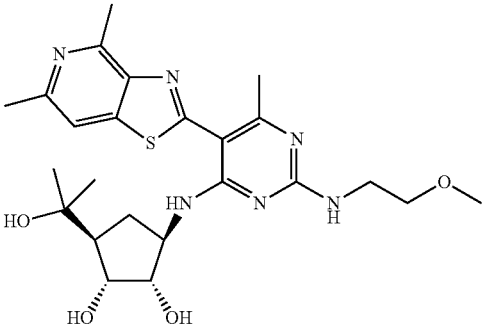
Compd #	Structure	LC-MS or MS $(M + H)^+$
3303		619.2
3304		591.2
3305		571.2
3306		503.2

TABLE IIIA-continued

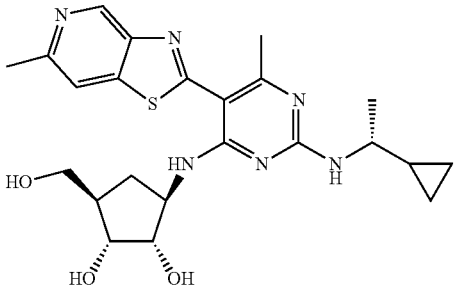
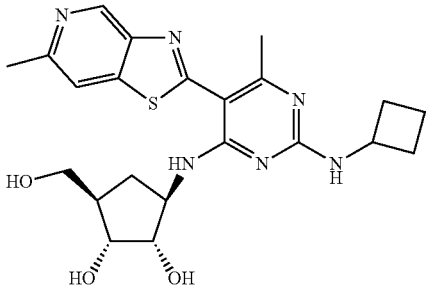
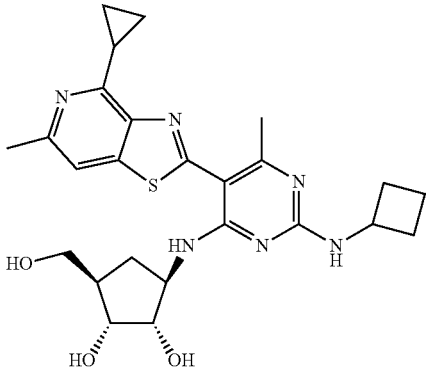
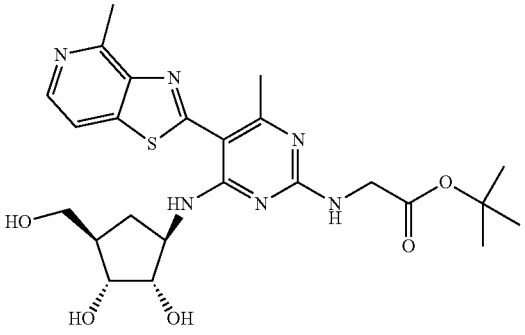
Compd #	Structure	LC-MS or MS $(M + H)^+$
3307		471.2
3308		457.2
3309		497.2
3310		517.2

TABLE IIIA-continued

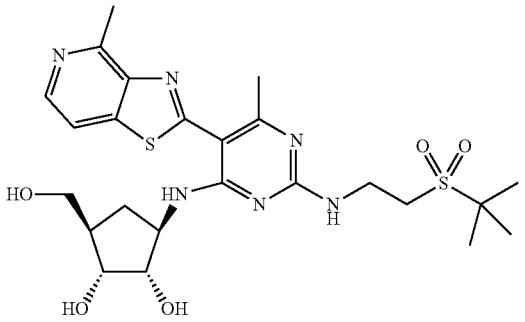
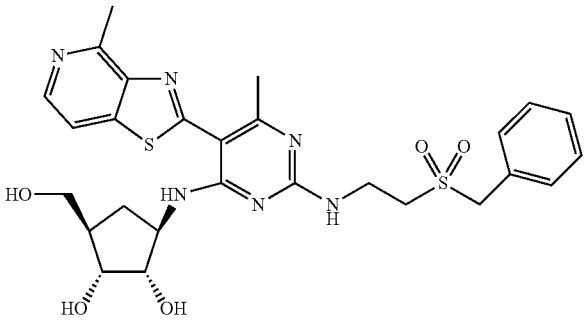
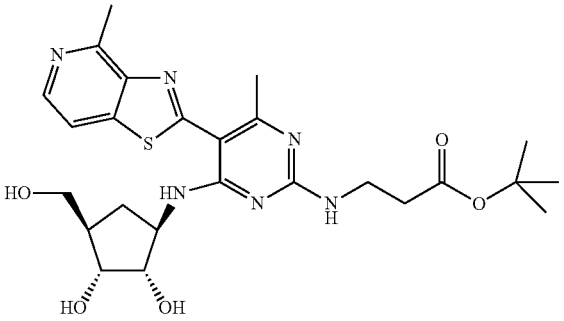
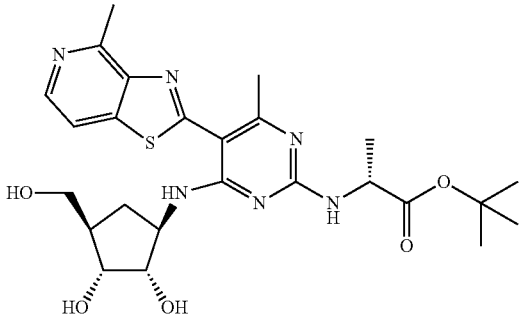
Compd #	Structure	LC-MS or MS (M + H)+
3313		
3314		585.1
3315		531.2
3316		531.2

TABLE IIIA-continued

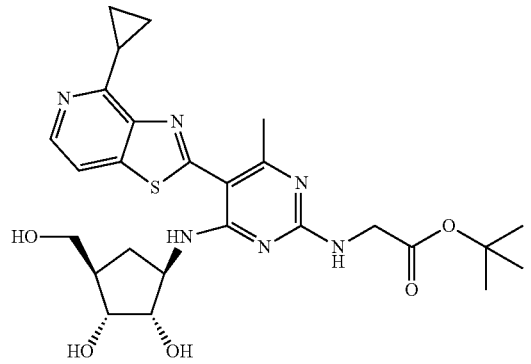
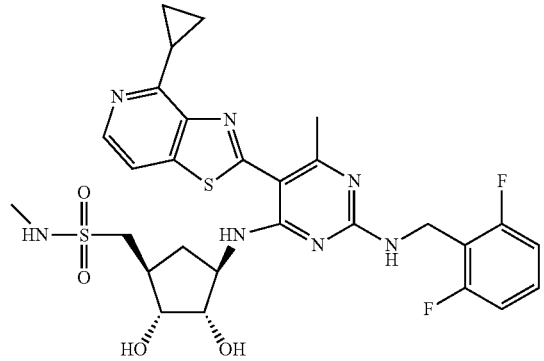
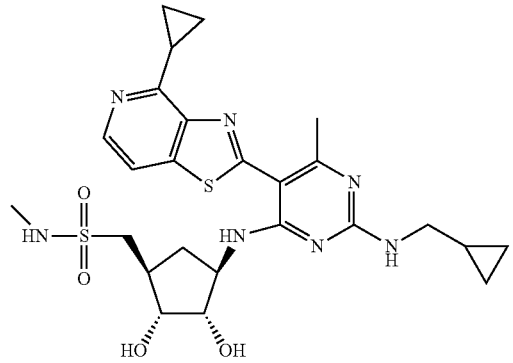
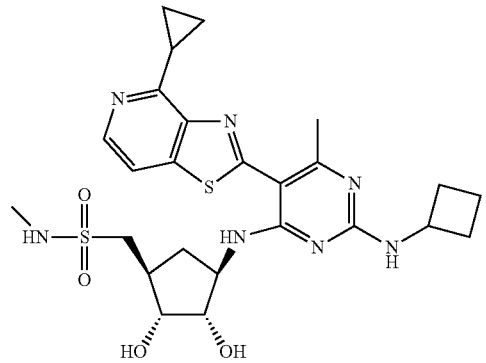
Compd #	Structure	LC-MS or MS $(M + H)^+$
3317		543.2
3318		632.2
3319		560.2
3320		560.0

TABLE IIIA-continued

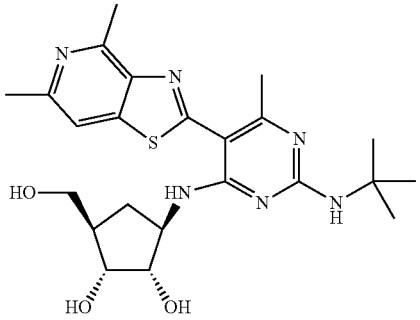
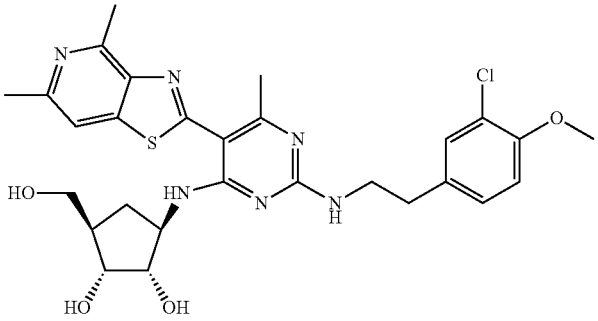
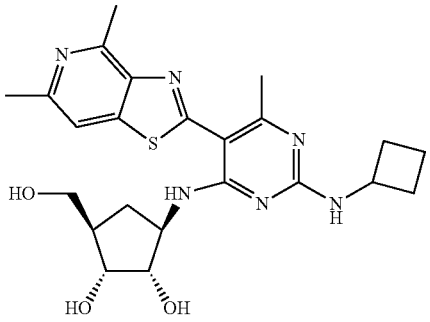
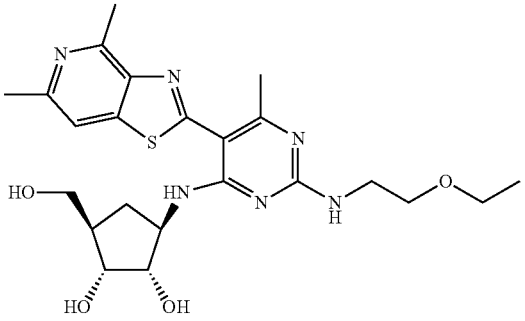
Compd #	Structure	LC-MS or MS $(M + H)^+$
3401		473.2
3402		585.2
3405		471.22
3408		489.2

TABLE IIIA-continued

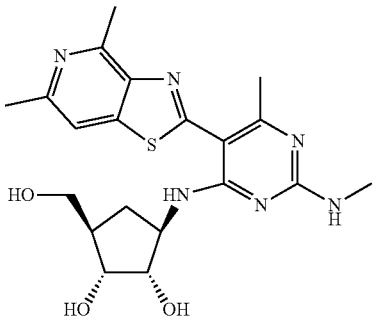
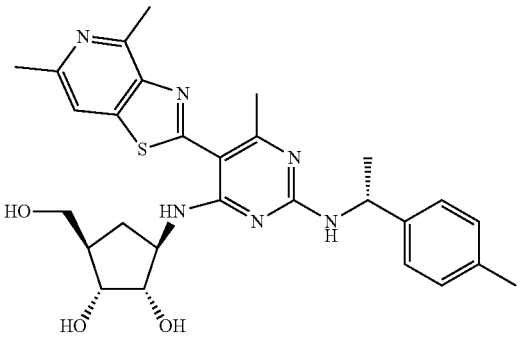
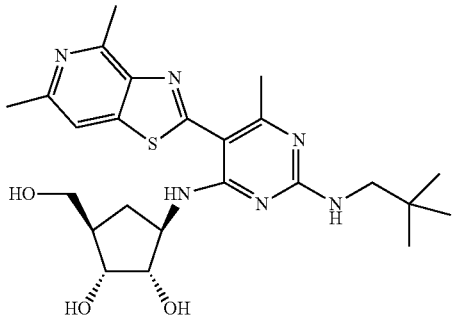
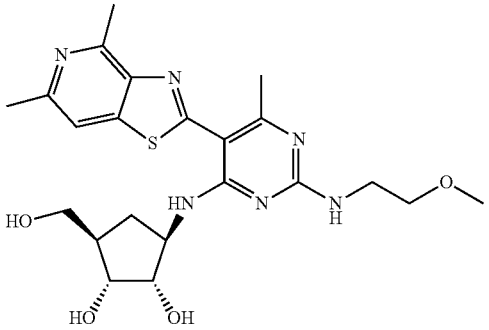
Compd #	Structure	LC-MS or MS $(M + H)^+$
3411		431.2
3412		535.2
3415		487.2
3416		475.2

TABLE IIIA-continued

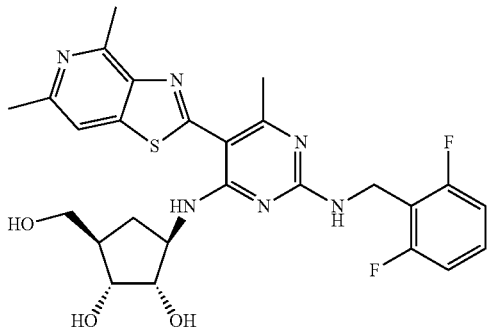
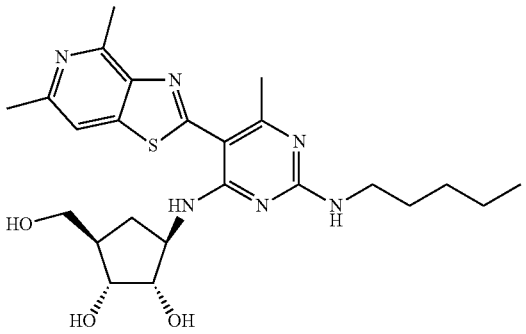
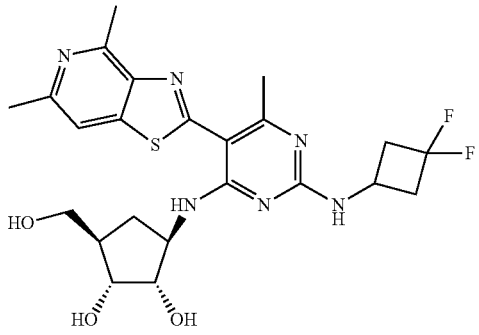
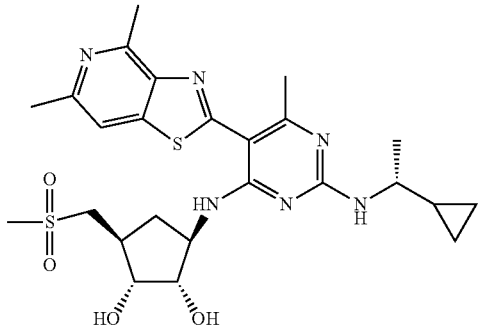
Compd #	Structure	LC-MS or MS $(M + H)^+$
3417		543.2
3418		487.2
3419		507.2
3421		547.2

TABLE IIIA-continued

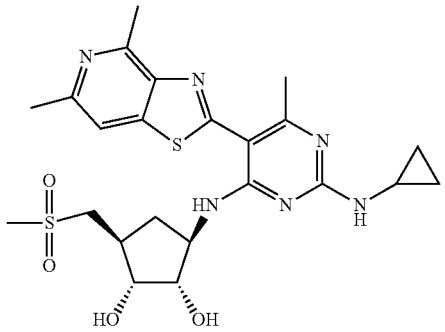
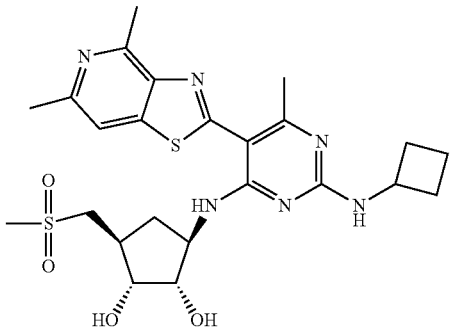
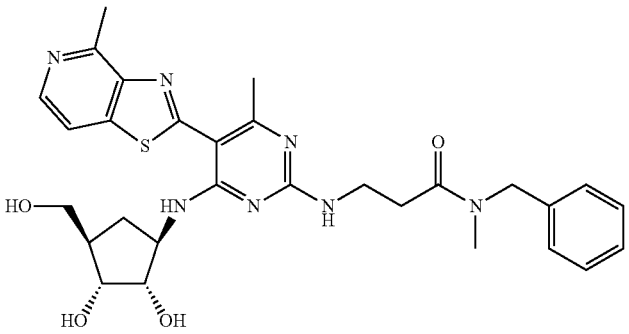
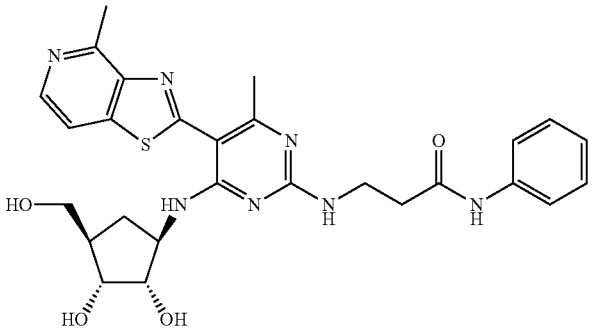
Compd #	Structure	LC-MS or MS $(M + H)^+$
3425		519.2
3426		533.2
3427		578.2
3428		550.2

TABLE IIIA-continued

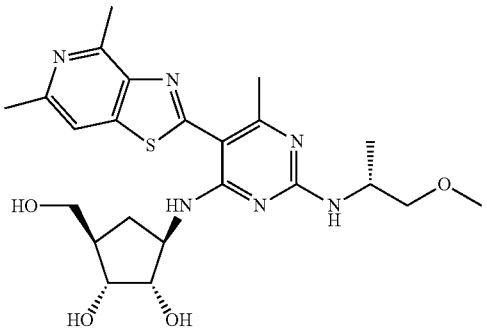
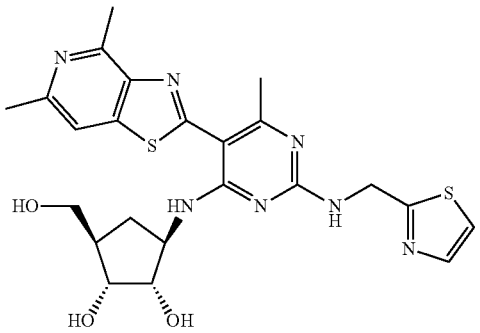
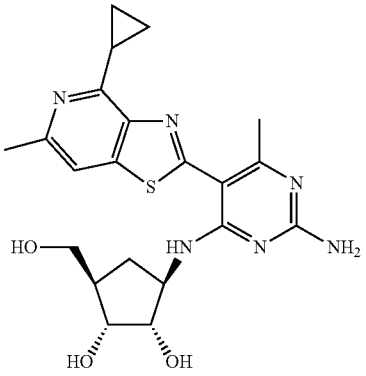
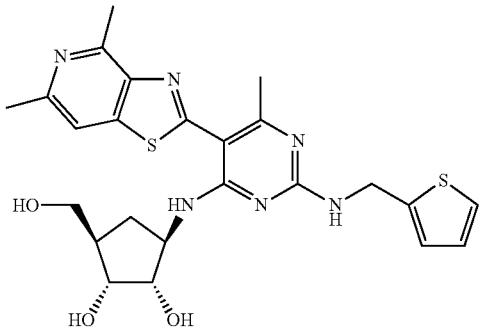
Compd #	Structure	LC-MS or MS $(M + H)^+$
3430		489.2
3431		514.1
3432		443.2
3433		513.2

TABLE IIIA-continued

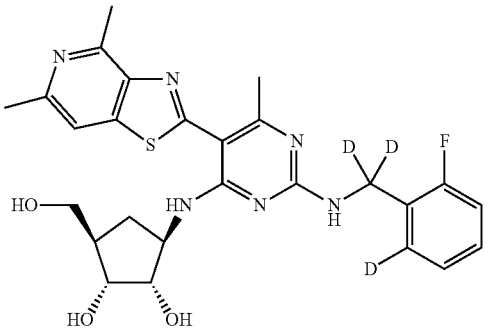
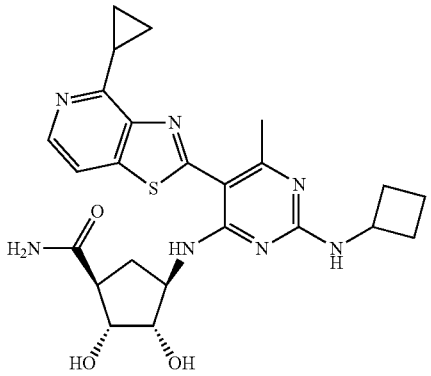
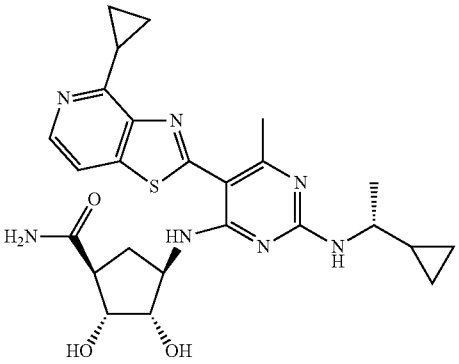
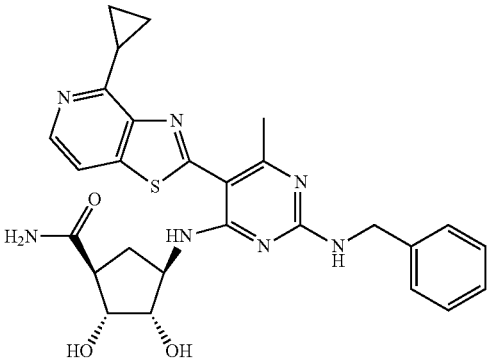
Compd #	Structure	LC-MS or MS $(M + H)^+$
3434		528.2
3435		496.2
3436		550.2
3437		532.2

TABLE IIIA-continued

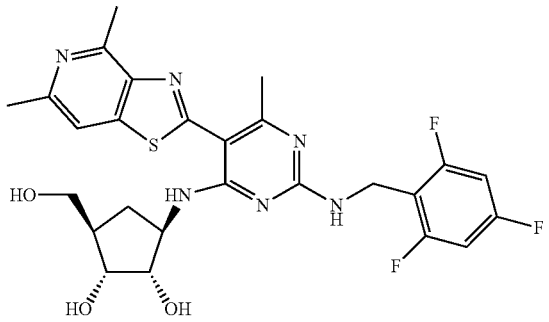
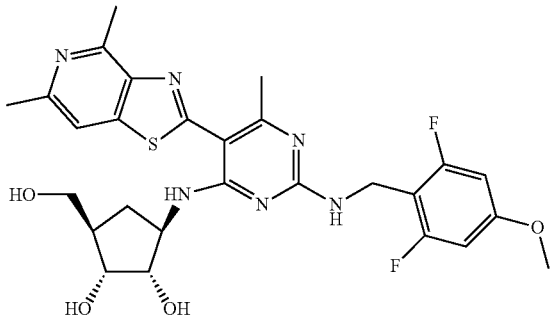
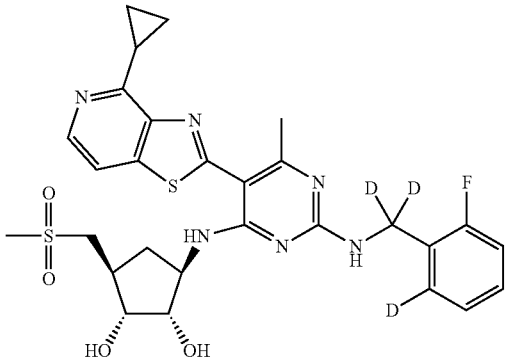
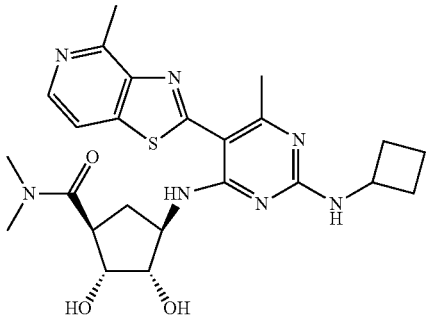
Compd #	Structure	LC-MS or MS $(M + H)^+$
3438		561.2
3439		573.2
3440		602.2
3441		498.2

TABLE IIIA-continued

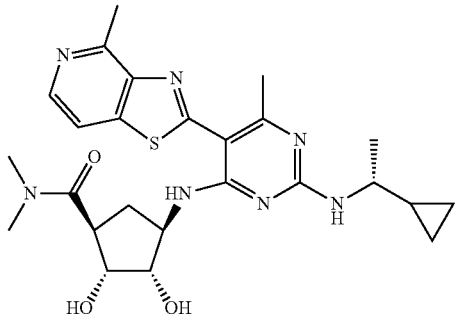
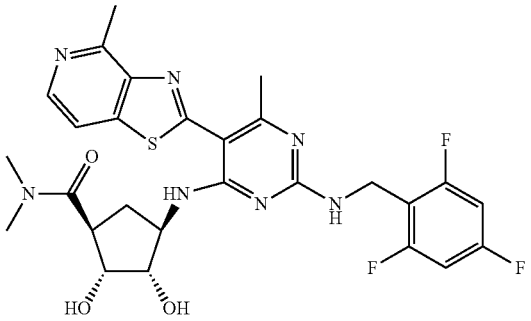
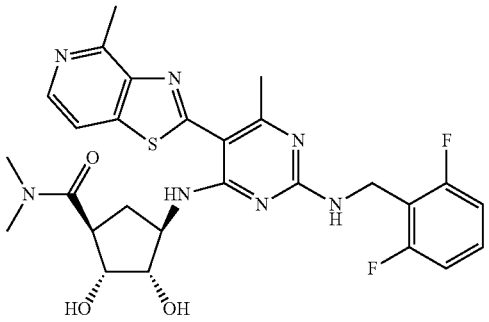
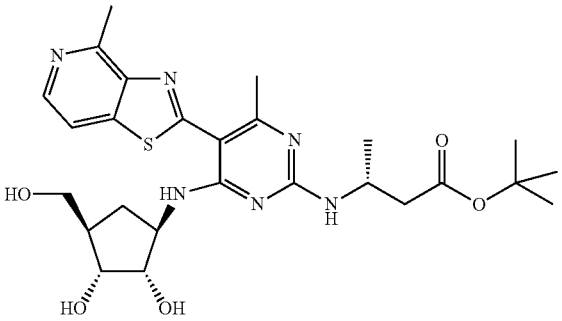
Compd #	Structure	LC-MS or MS $(M + H)^+$
3442		512.2
3443		588.2
3444		570.2
3445		545.2

TABLE IIIA-continued

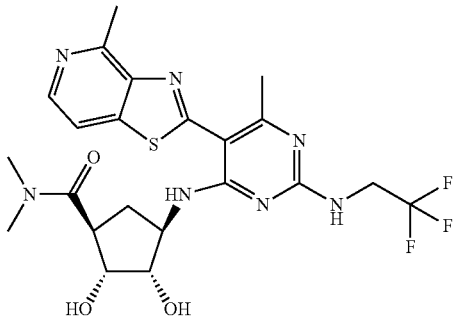
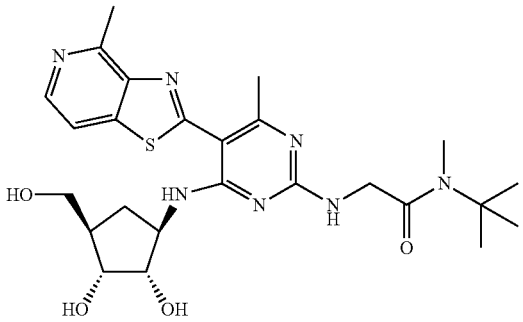
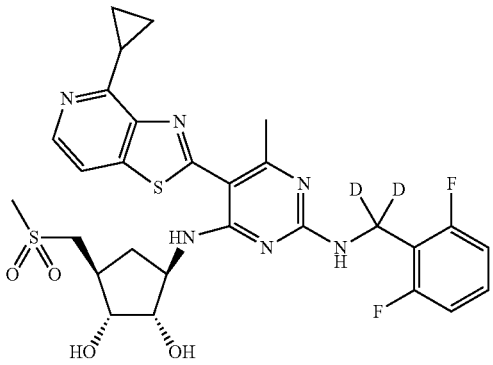
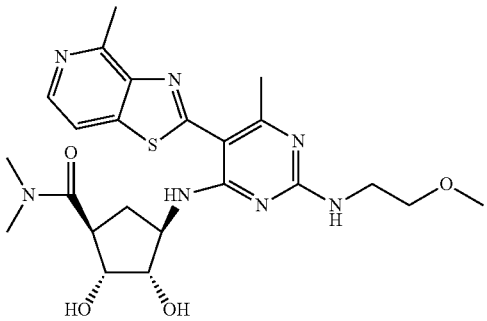
Compd #	Structure	LC-MS or MS $(M + H)^+$
3446		526.2
3447		530.2
3448		619.2
3449		502.2

TABLE IIIA-continued

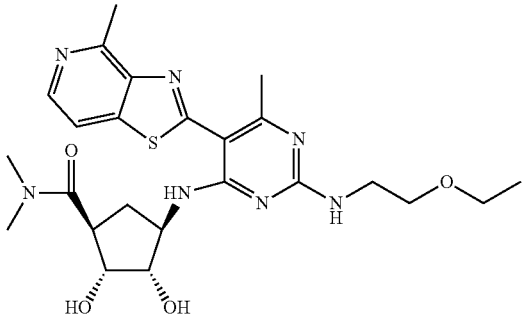
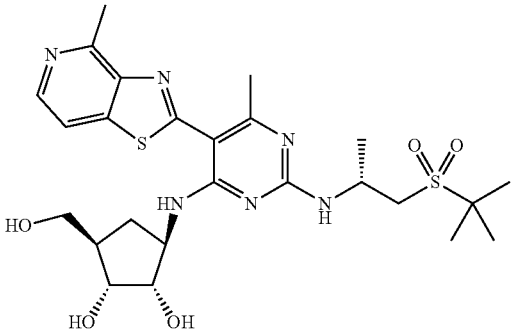
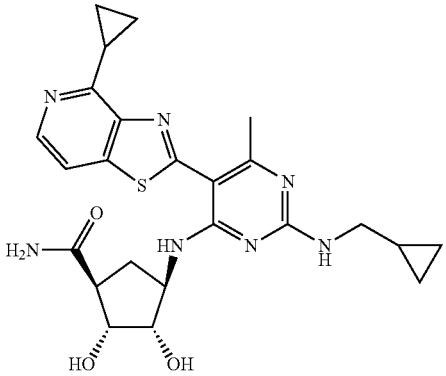
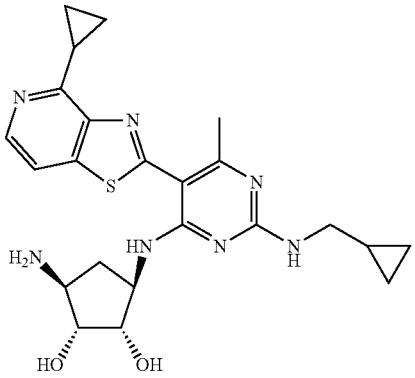
Compd #	Structure	LC-MS or MS $(M + H)^+$
3450		516.2
3451		565.0
3453		496.2
3454		468.2

TABLE IIIA-continued

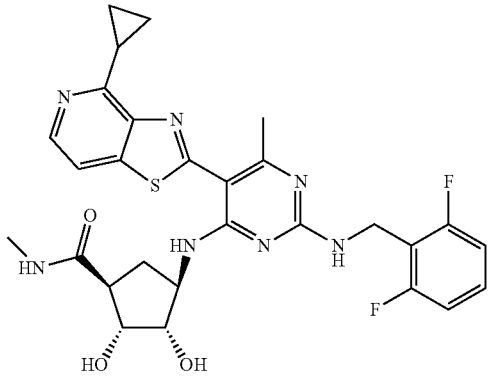
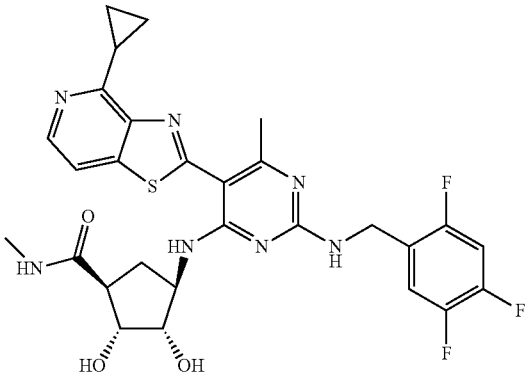
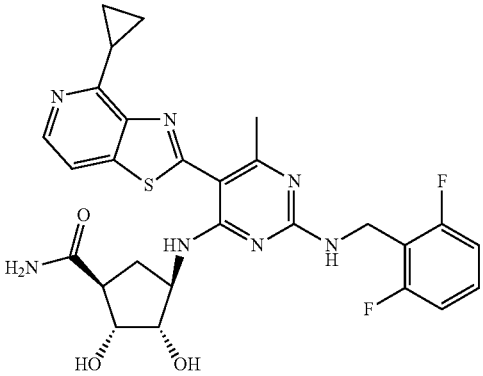
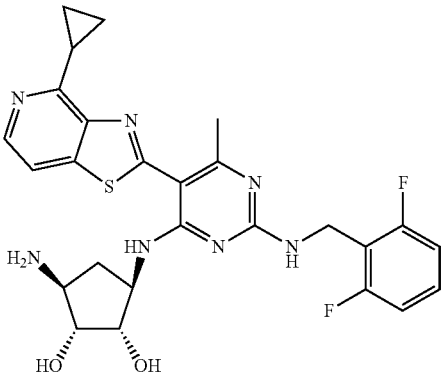
Compd #	Structure	LC-MS or MS $(M + H)^+$
3455		582.2
3456		600.2
3457		568.2
3458		540.2

TABLE IIIA-continued

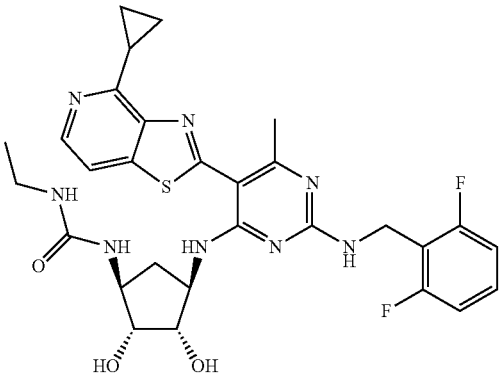
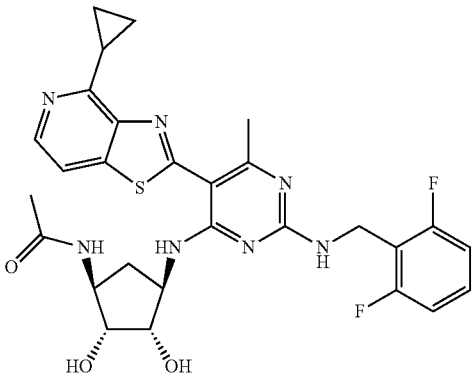
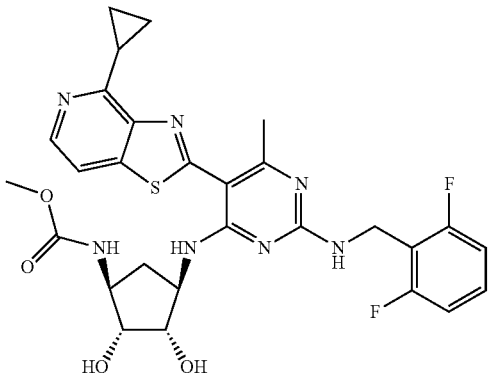
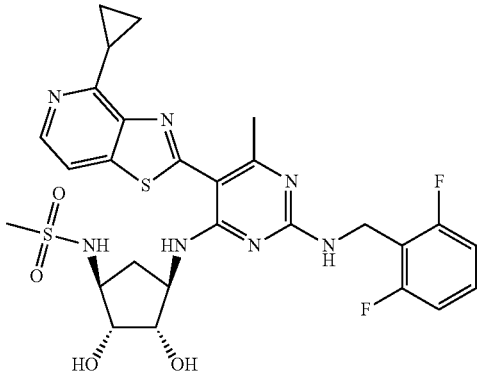
Compd #	Structure	LC-MS or MS $(M + H)^+$
3459		611.2
3460		582.2
3461		598.2
3462		618.0

TABLE IIIA-continued

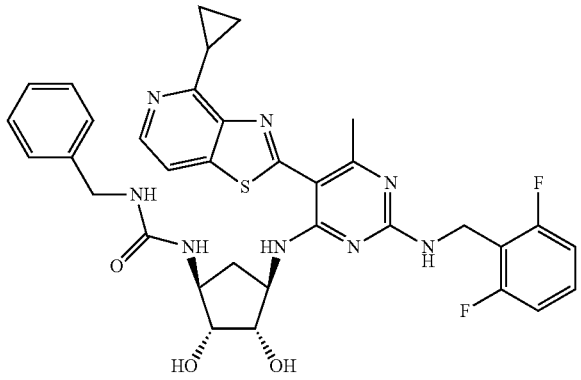
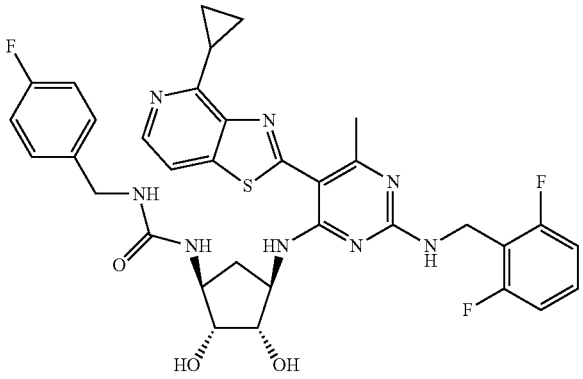
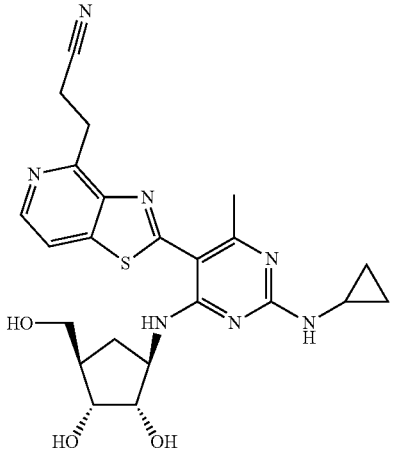
Compd #	Structure	LC-MS or MS $(M + H)^+$
3463		673.0
3464		690.0
3501		482.4

TABLE IIIA-continued

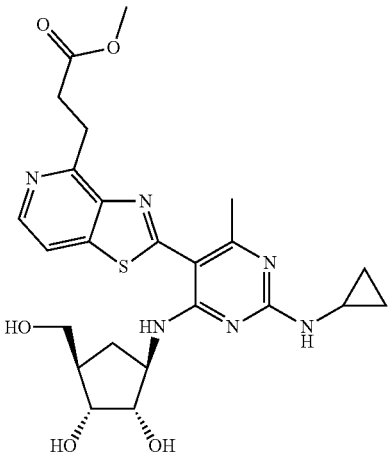
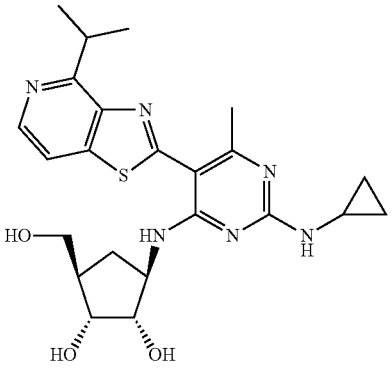
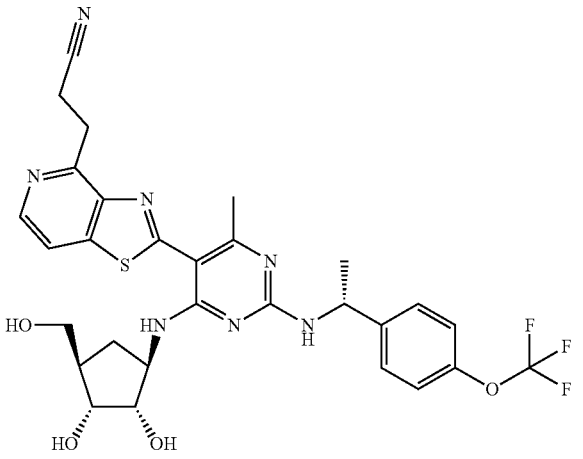
Compd #	Structure	LC-MS or MS $(M + H)^+$
3502		515.4
3503		471.4
3504		630.5

TABLE IIIA-continued

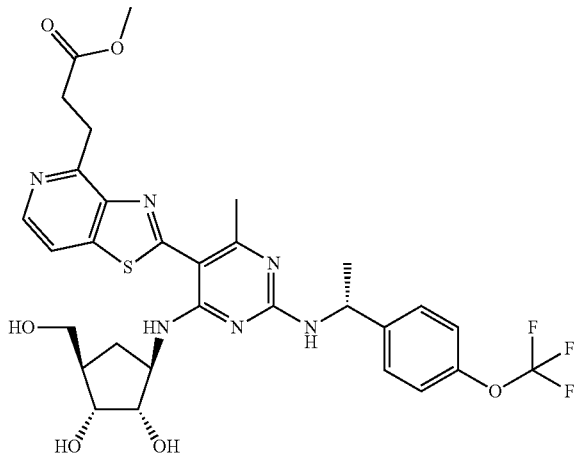
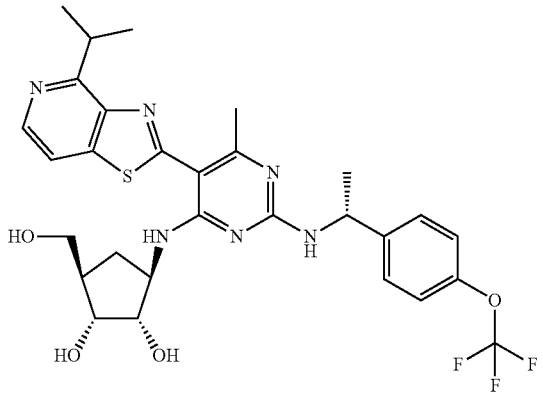
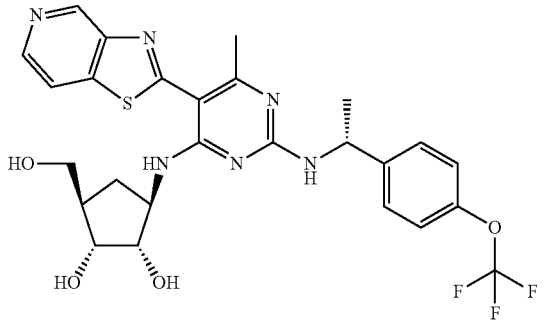
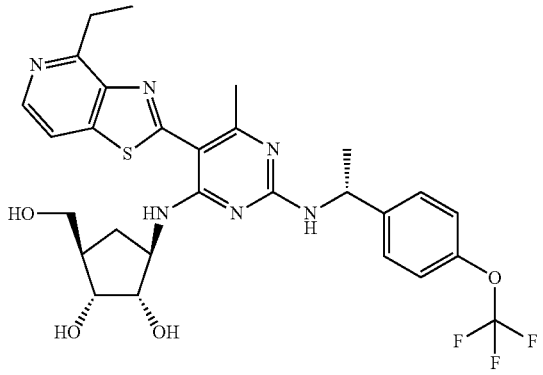
Compd #	Structure	LC-MS or MS $(M + H)^+$
3505		663.5
3506		619.5
3507		577.3
3508		605.3

TABLE IIIA-continued

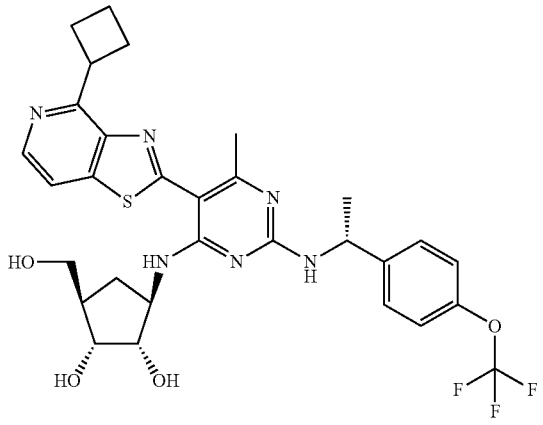
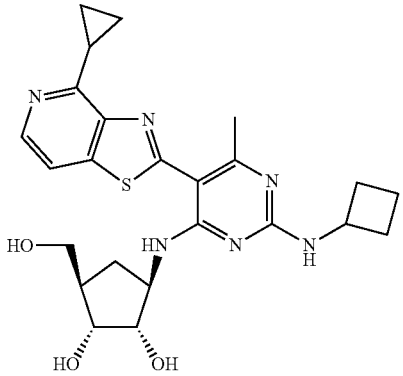
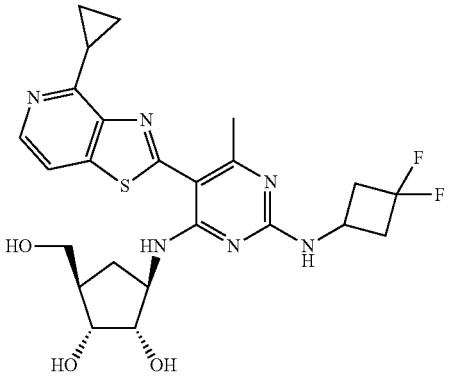
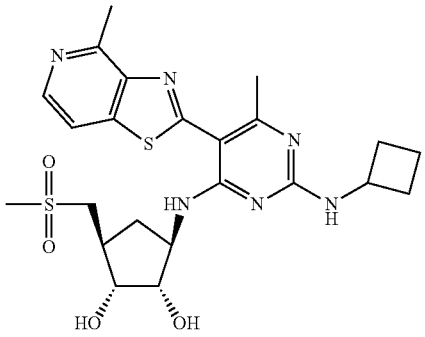
Compd #	Structure	LC-MS or MS $(M + H)^+$
3509		631.3
3510		483.3
3511		519.3
3512		519.3

TABLE IIIA-continued

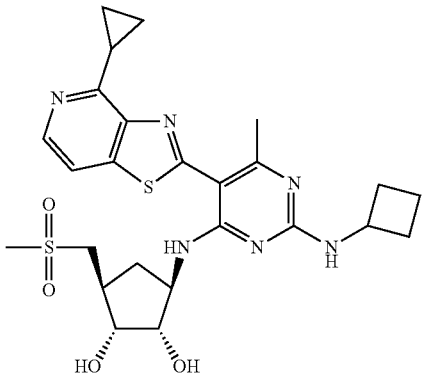
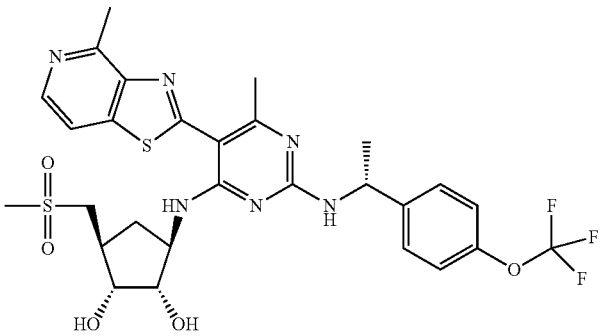
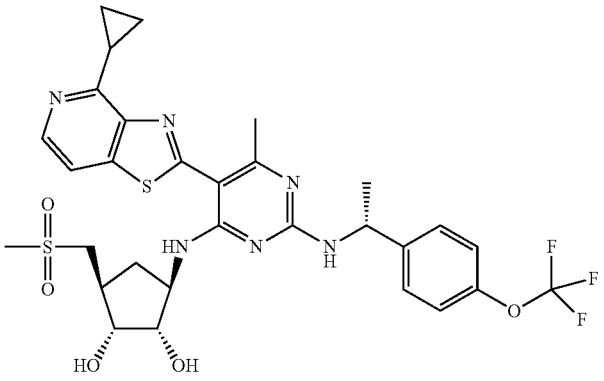
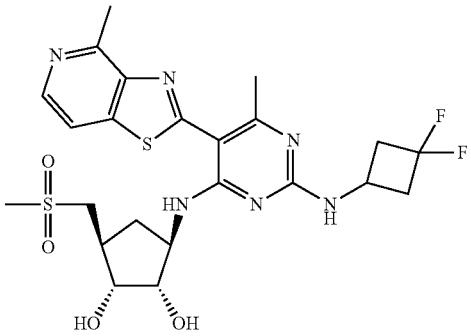
Compd #	Structure	LC-MS or MS $(M + H)^+$
3513		545.3
3514		653.3
3515		679.4
3516		555.3

TABLE IIIA-continued

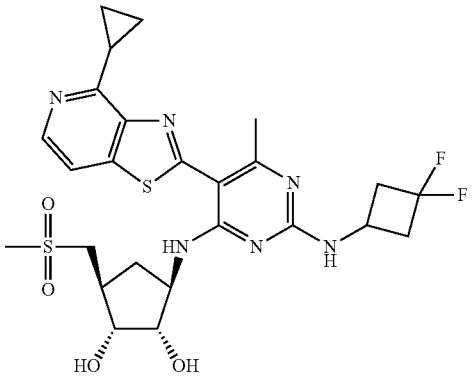
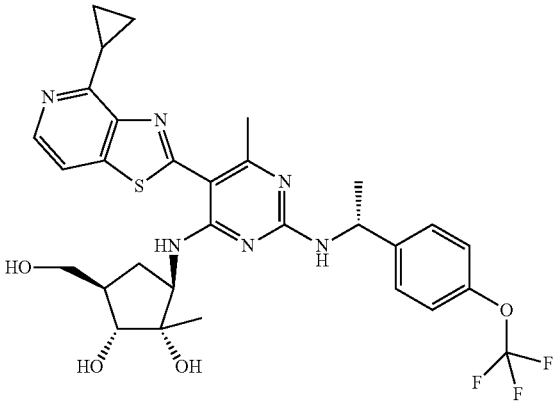
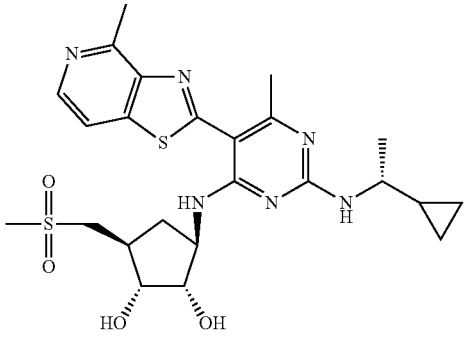
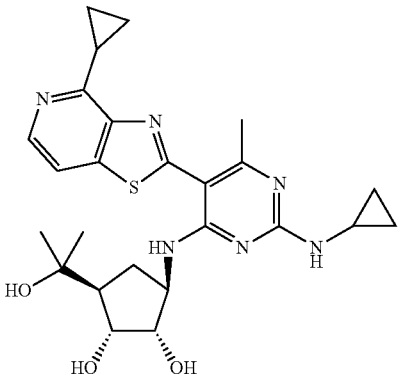
Compd #	Structure	LC-MS or MS $(M + H)^+$
3517		581.3
3518		631.3
3519		533.3
3520		497.3

TABLE IIIA-continued

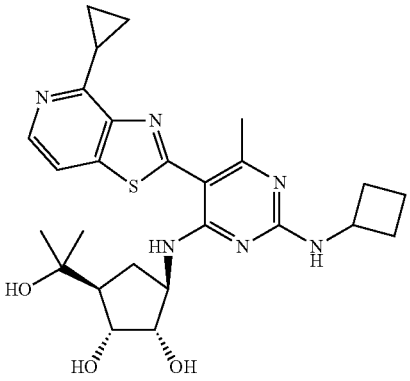
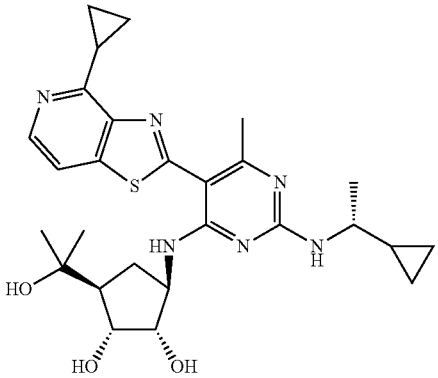
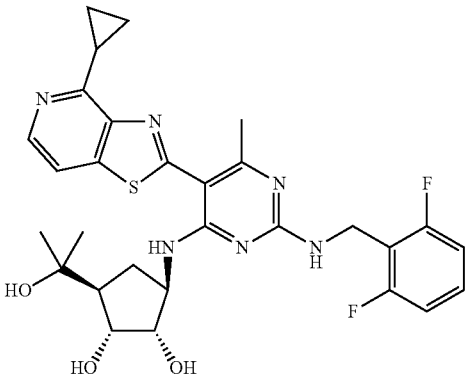
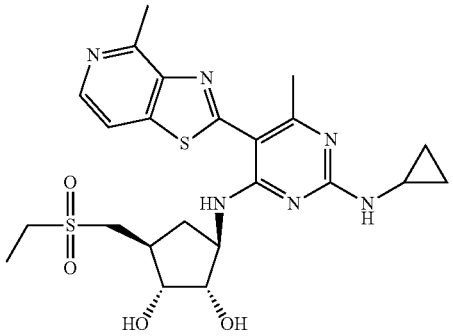
Compd #	Structure	LC-MS or MS $(M + H)^+$
3521		511.4
3522		525.4
3523		583.4
3524		519.3

TABLE IIIA-continued

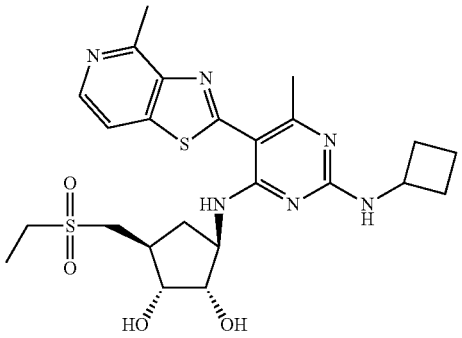
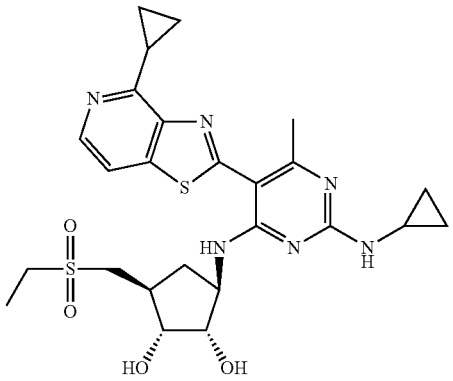
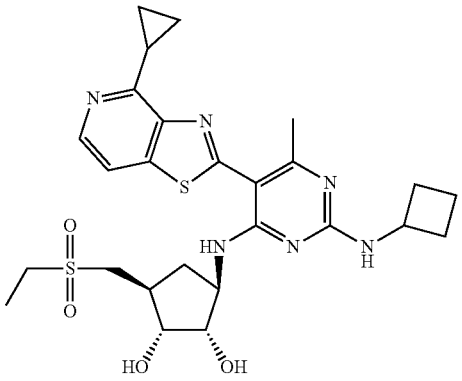
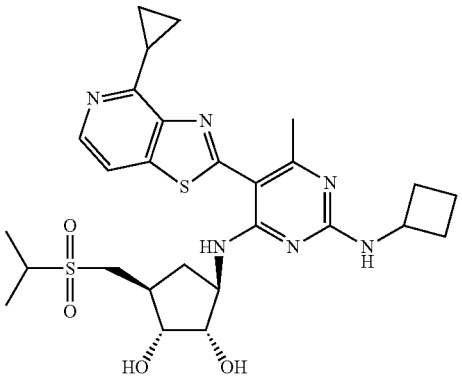
Compd #	Structure	LC-MS or MS $(M + H)^+$
3525		533.3
3526		545.3
3527		559.3
3528		573.3

TABLE IIIA-continued

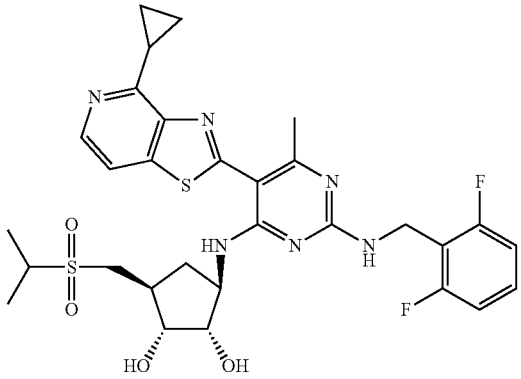
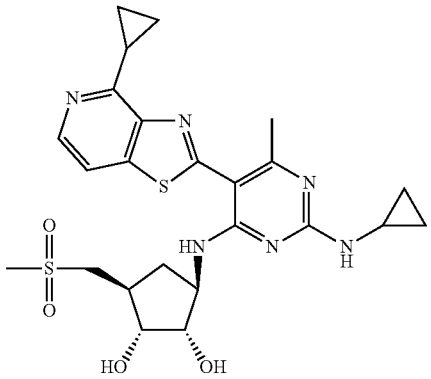
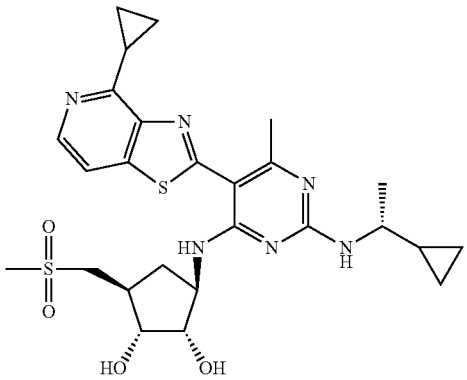
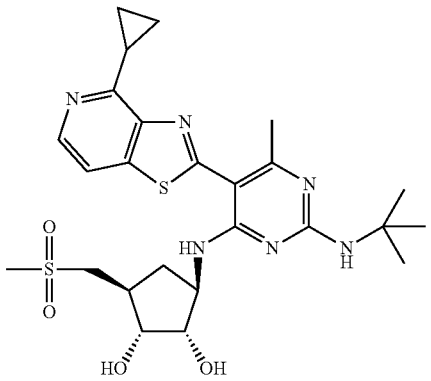
Compd #	Structure	LC-MS or MS $(M + H)^+$
3529		645.3
3530		531.3
3531		559.4
3532		547.3

TABLE IIIA-continued

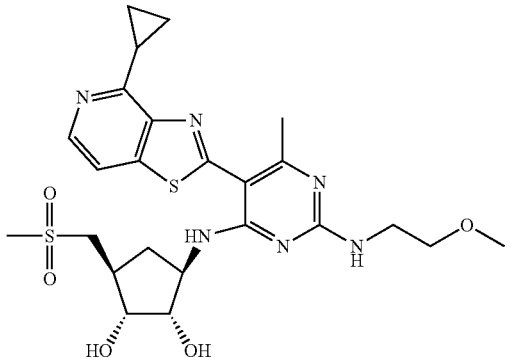
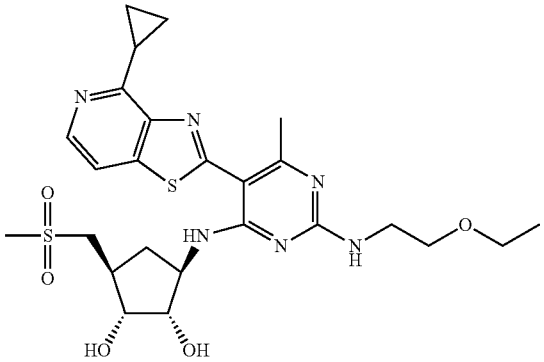
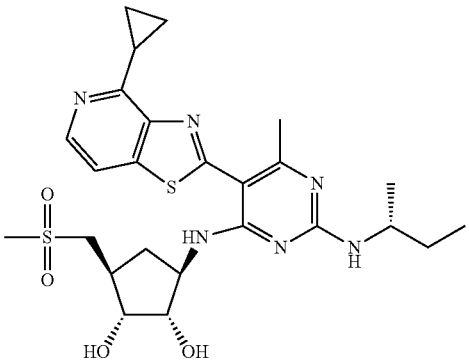
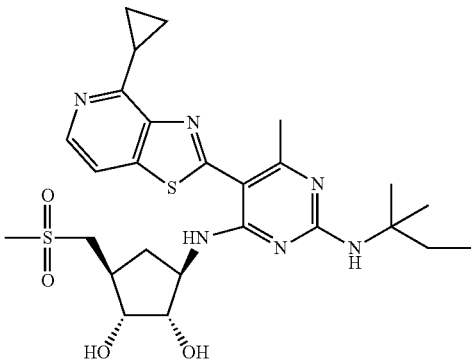
Compd #	Structure	LC-MS or MS $(M + H)^+$
3533		549.4
3534		563.4
3535		547.3
3536		561.4

TABLE IIIA-continued

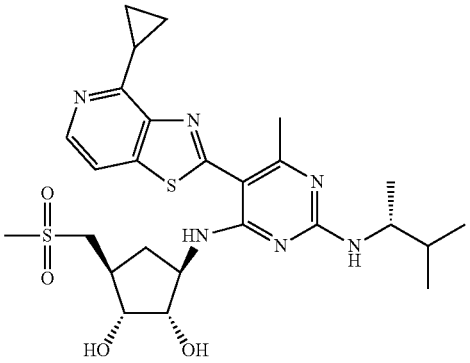
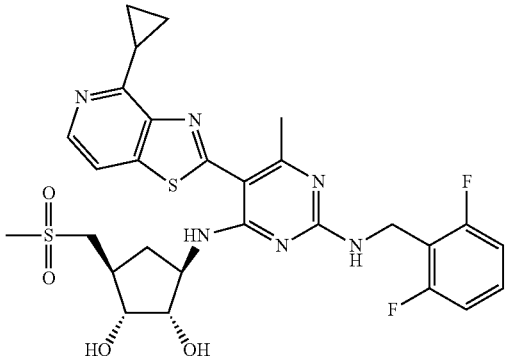
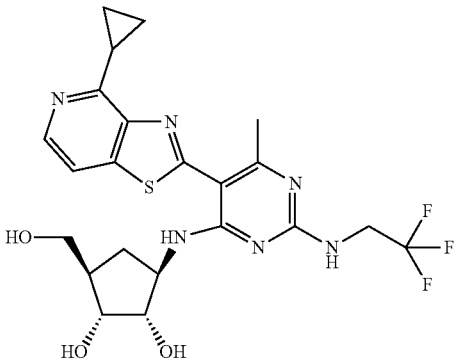
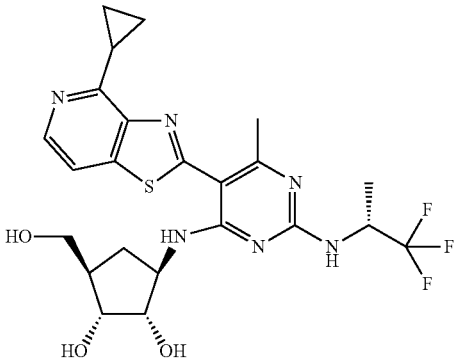
Compd #	Structure	LC-MS or MS $(M + H)^+$
3537		561.4
3538		617.4
3539		511.3
3540		525.3

TABLE IIIA-continued

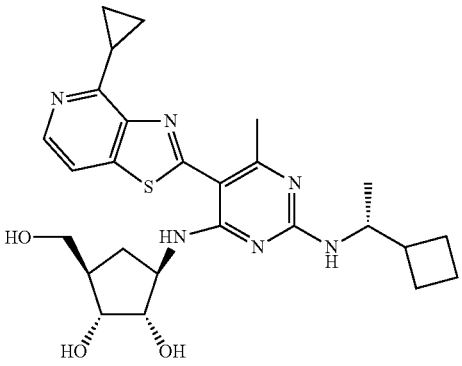
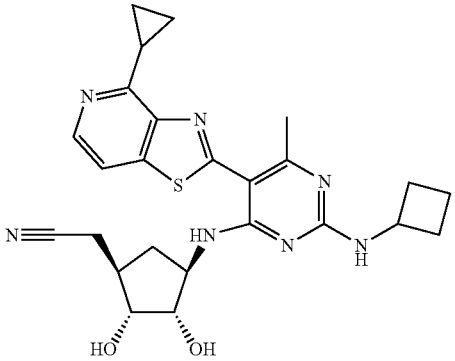
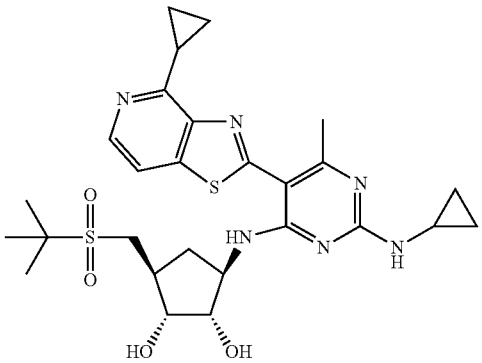
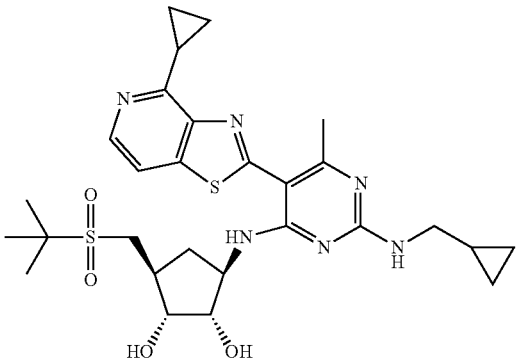
Compd #	Structure	LC-MS or MS $(M + H)^+$
3541		511.4
3542		492.3
3543		573.4
3544		587.4

TABLE IIIA-continued

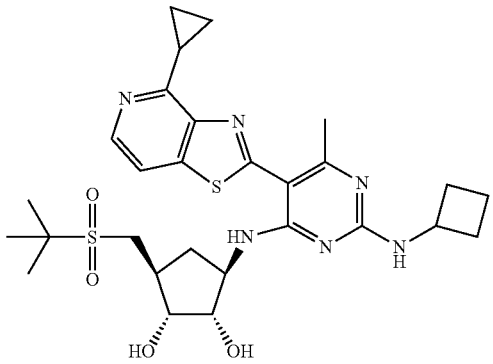
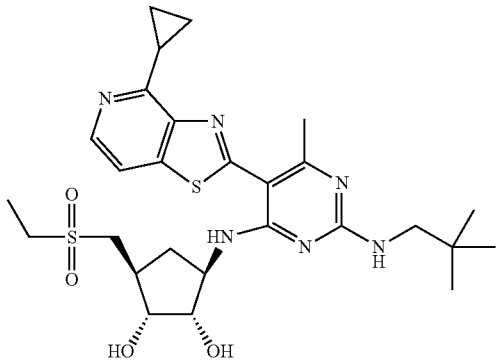
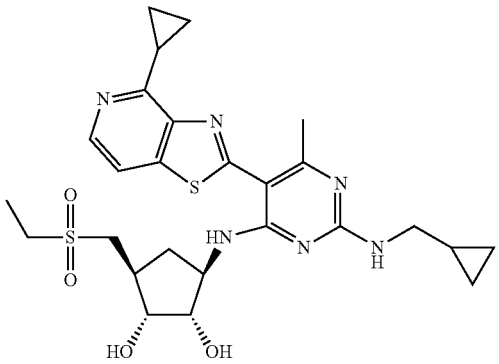
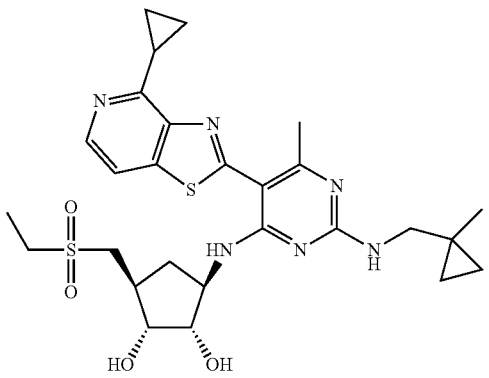
Compd #	Structure	LC-MS or MS $(M + H)^+$
3545		587.4
3546		575.4
3547		559.3
3548		573.4

TABLE IIIA-continued

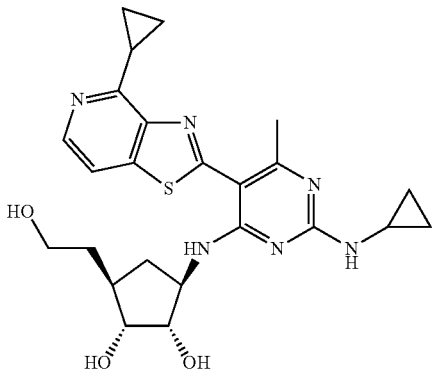
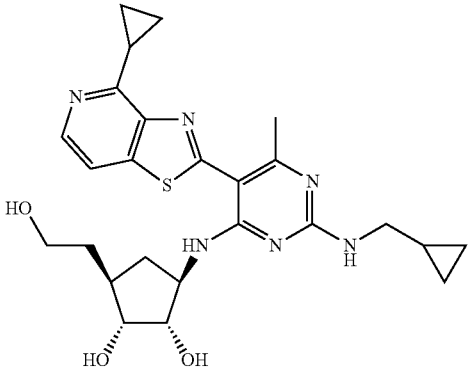
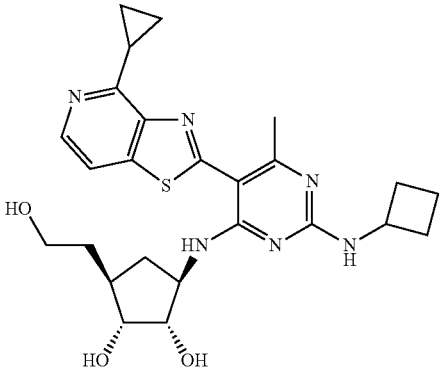
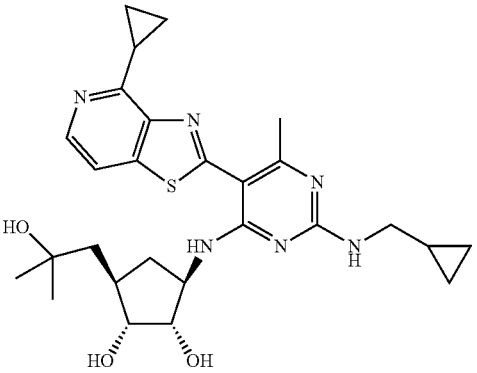
Compd #	Structure	LC-MS or MS $(M + H)^+$
3549		457.3
3550		471.2
3551		471.2
3552		499.4

TABLE IIIA-continued

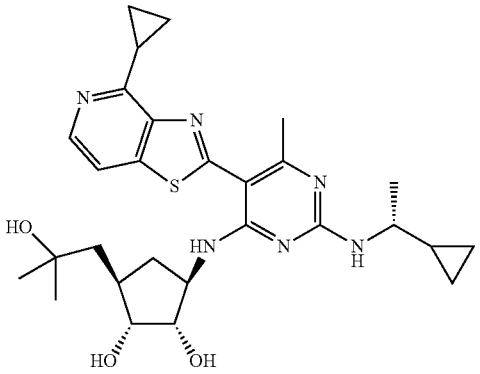
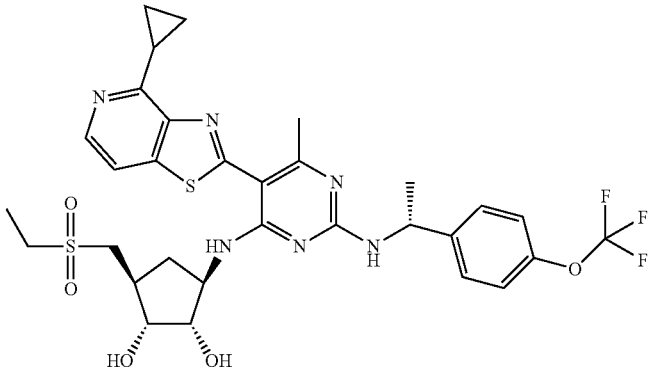
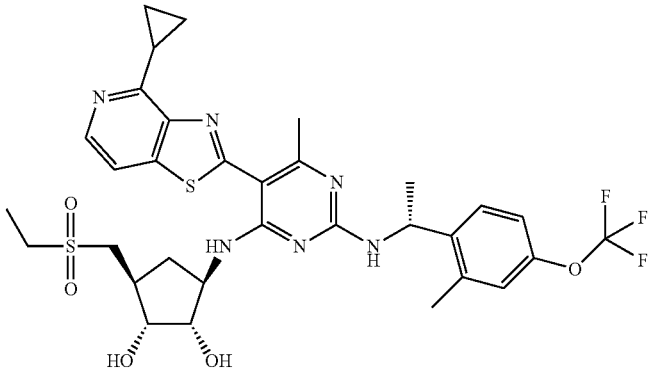
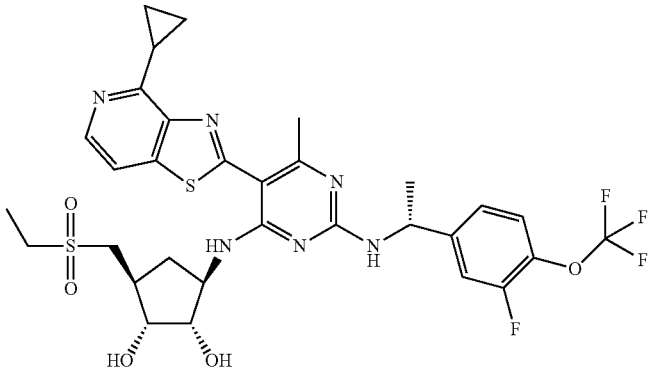
Compd #	Structure	LC-MS or MS $(M + H)^+$
3553		513.4
3554		693.4
3555		707.5
3556		711.3

TABLE IIIA-continued

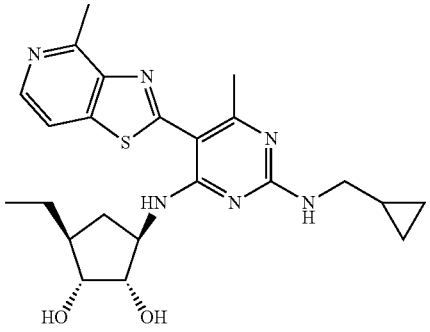
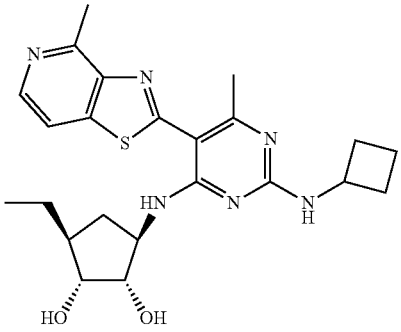
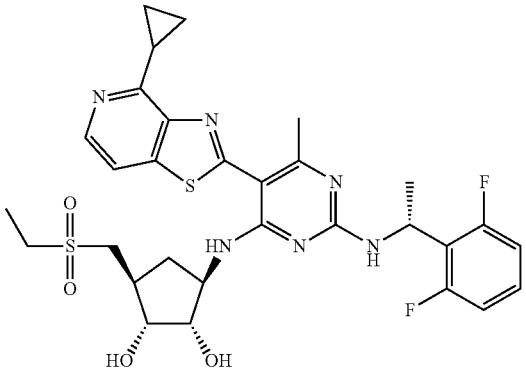
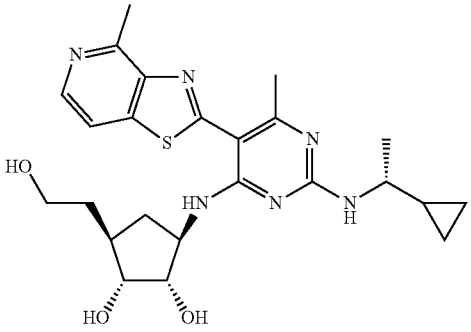
Compd #	Structure	LC-MS or MS $(M + H)^+$
3557		455.3
3558		455.3
3560		645.4
3561		485.4

TABLE IIIA-continued

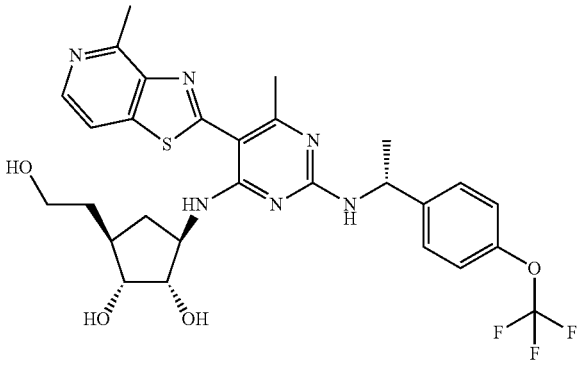
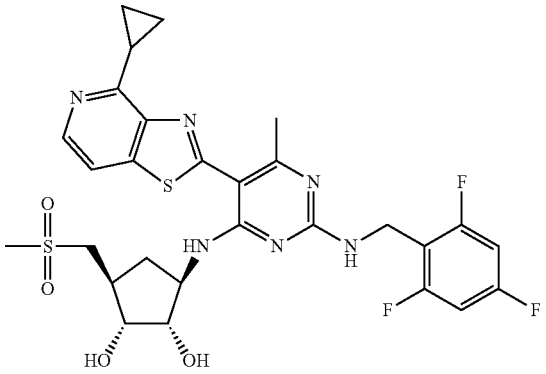
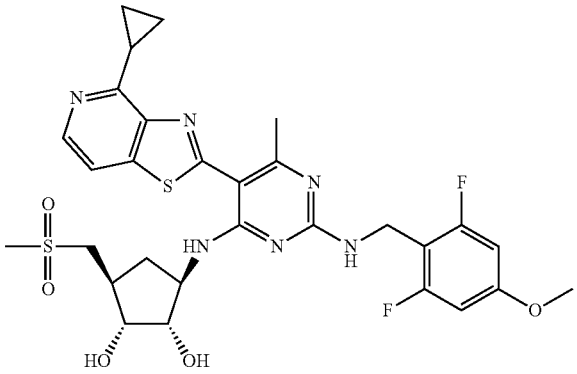
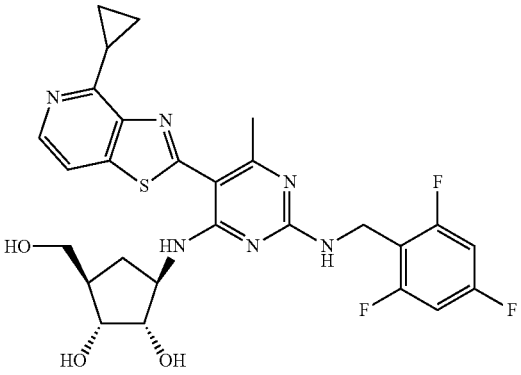
Compd #	Structure	LC-MS or MS $(M + H)^+$
3562		605.4
3563		635.3
3564		647.4
3565		573.3

TABLE IIIA-continued

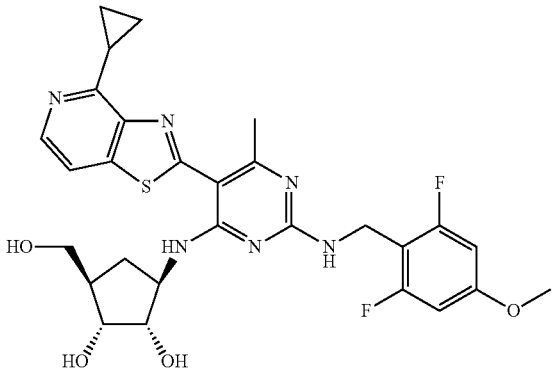
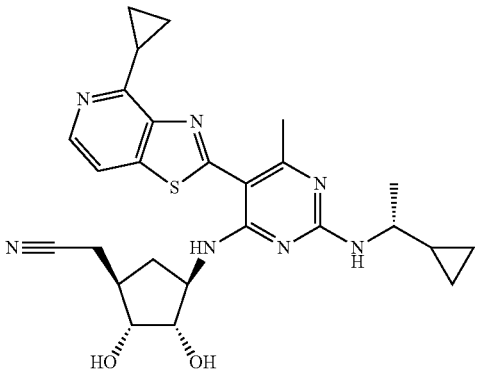
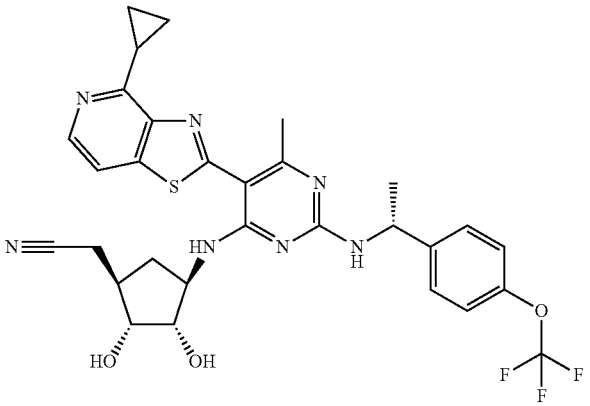
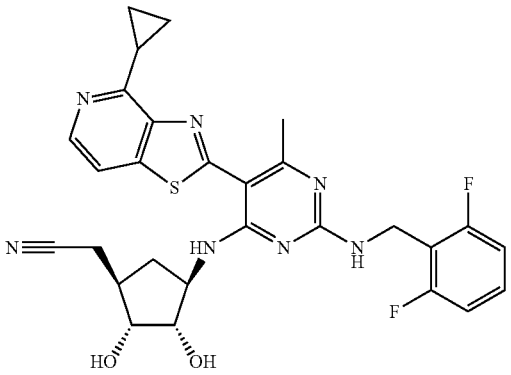
Compd #	Structure	LC-MS or MS $(M + H)^+$
3566		585.3
3567		506.4
3568		626.4
3569		564.3

TABLE IIIA-continued

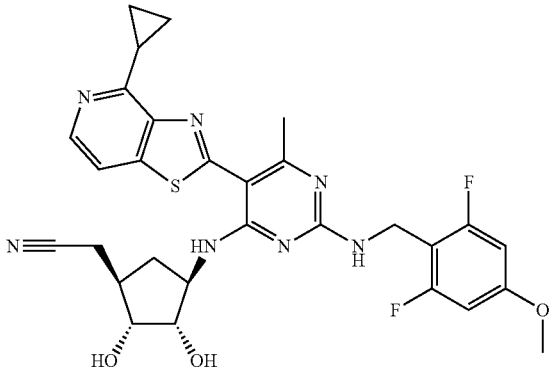
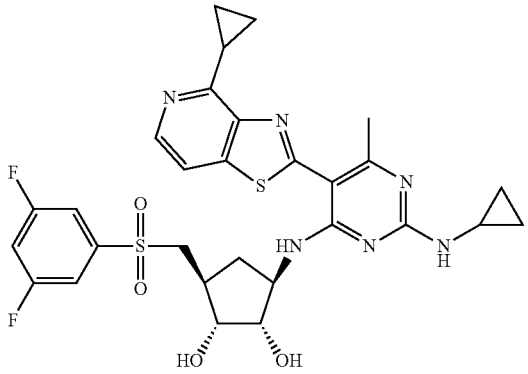
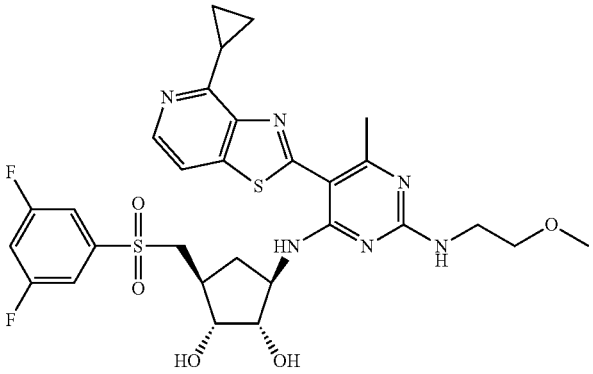
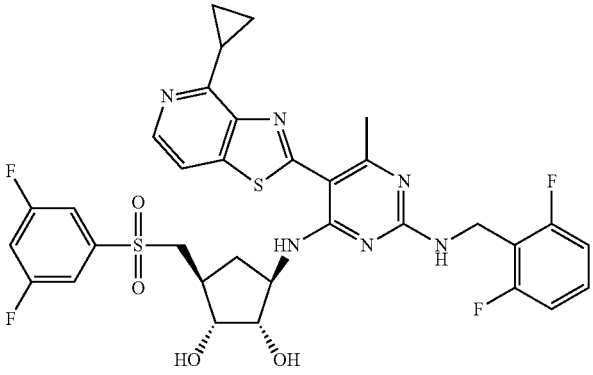
Compd #	Structure	LC-MS or MS $(M + H)^+$
3570		594.3
3571		629.0
3573		661.0
3574		715.0

TABLE IIIA-continued

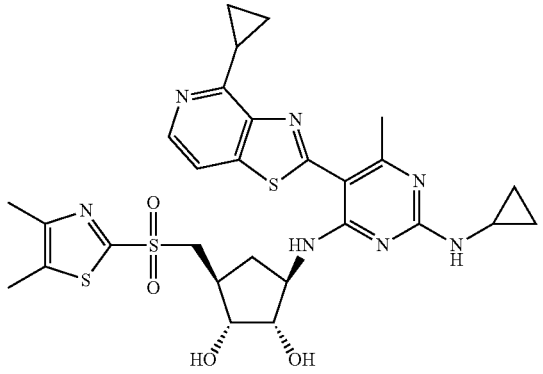
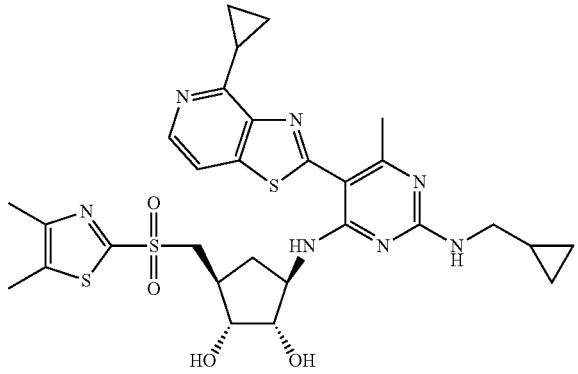
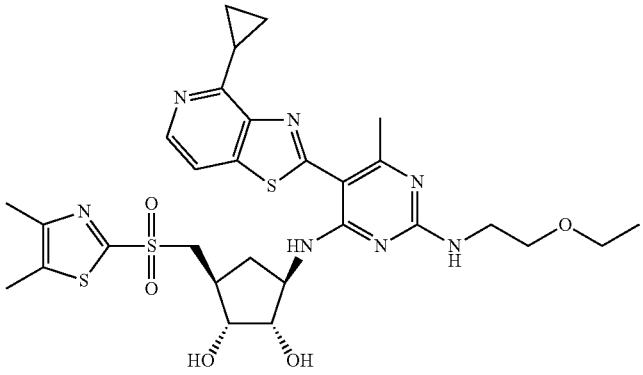
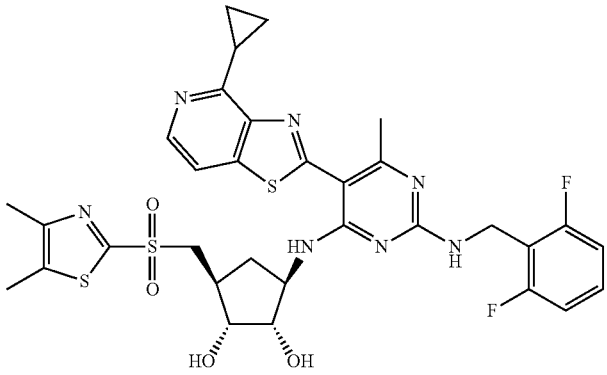
Compd #	Structure	LC-MS or MS $(M + H)^+$
3575		628.0
3576		642.1
3577		660.0
3578		714.0

TABLE IIIA-continued

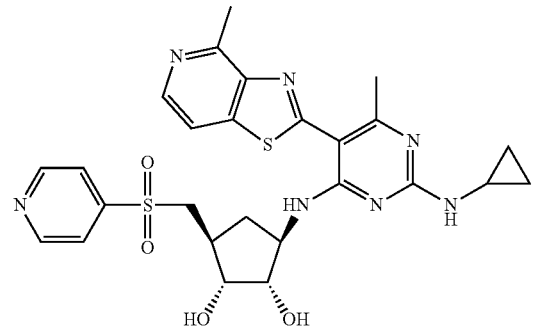
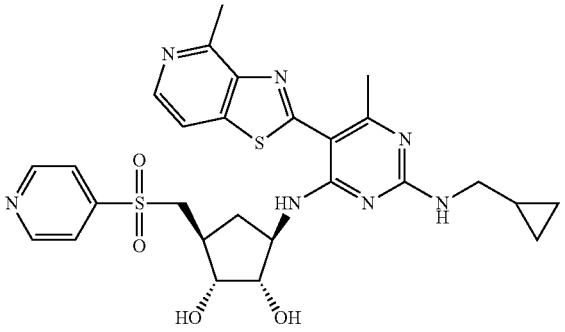
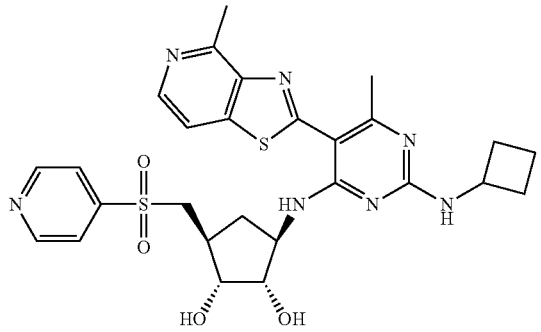
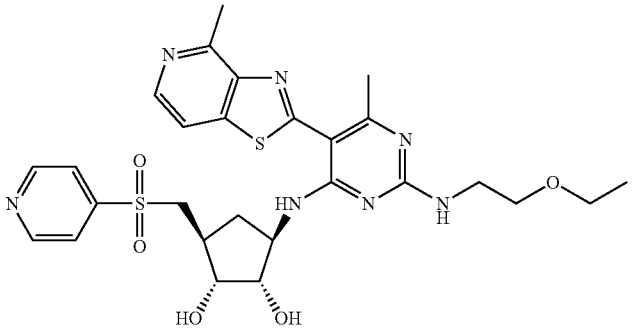
Compd #	Structure	LC-MS or MS $(M + H)^+$
3579		568.0
3580		582.1
3581		582.1
3582		600.2

TABLE IIIA-continued

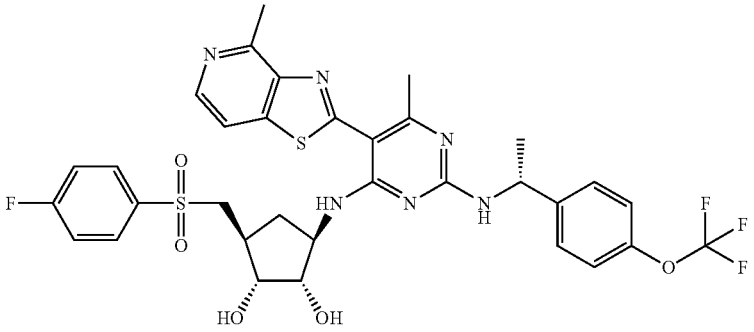
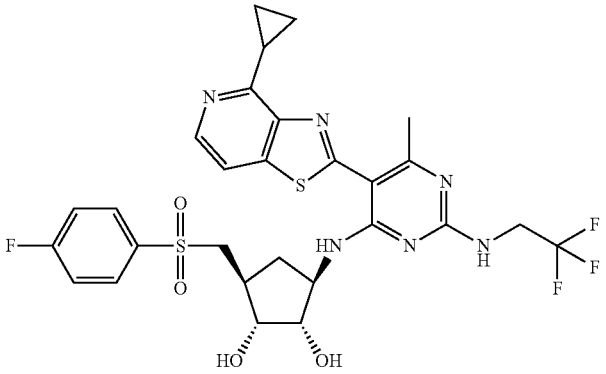
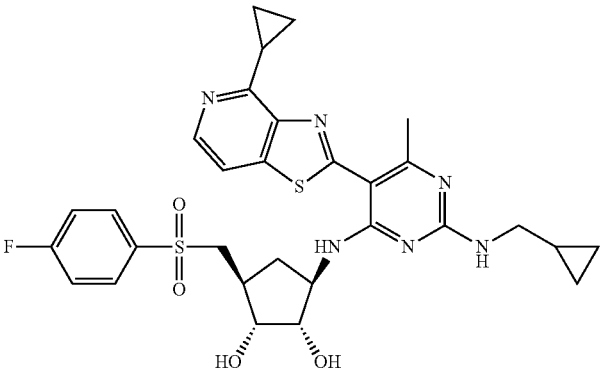
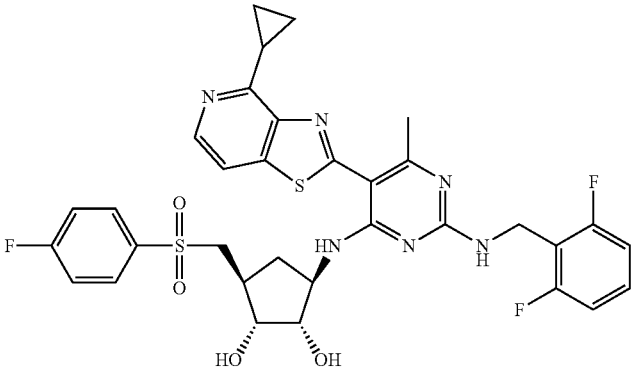
Compd #	Structure	LC-MS or MS $(M + H)^+$
3583		733.0
3584		653.0
3585		625.2
3586		697.0

TABLE IIIA-continued

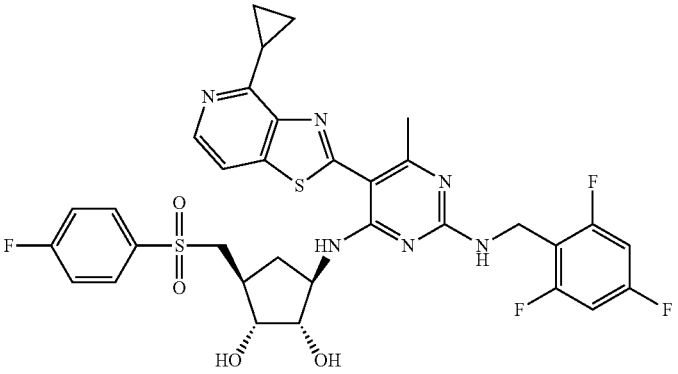
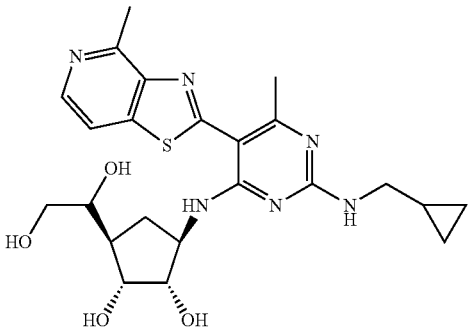
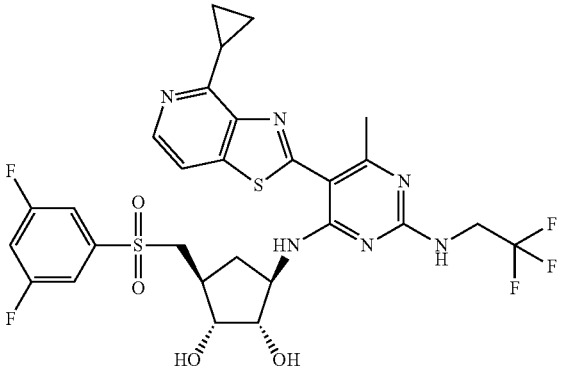
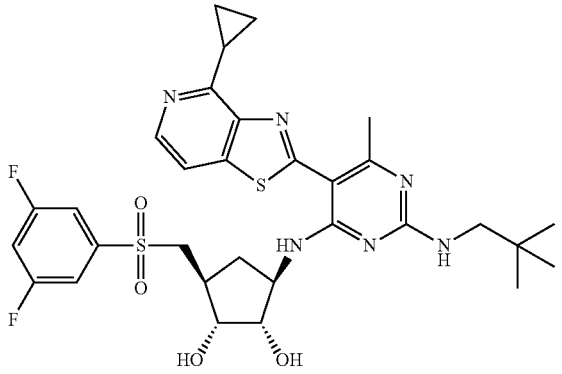
Compd #	Structure	LC-MS or MS $(M + H)^+$
3587		715.0
3591		487.2
3592		671.0
3593		659.2

TABLE IIIA-continued

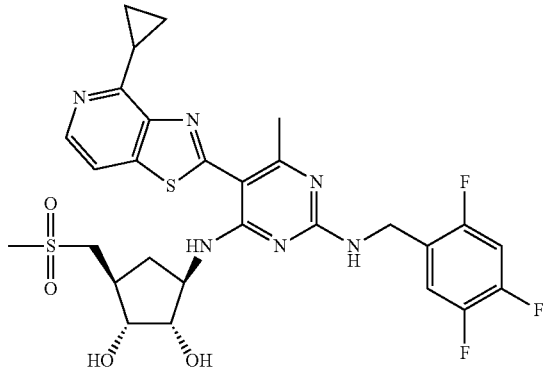
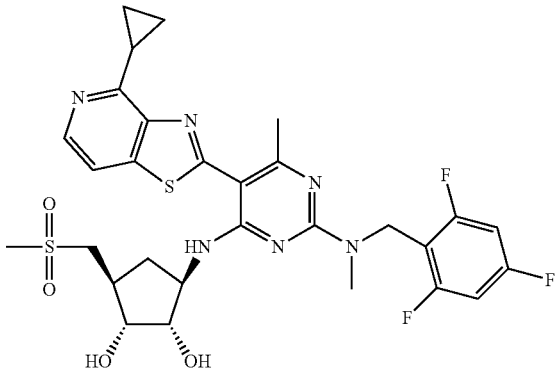
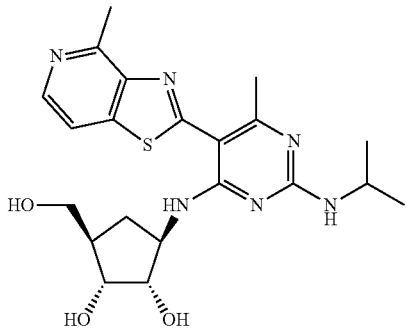
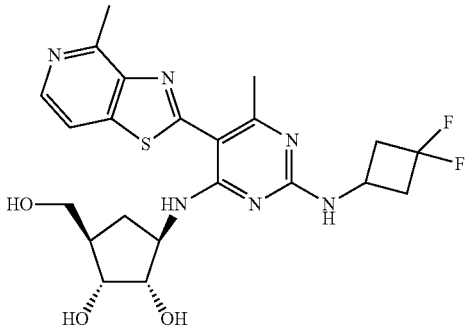
Compd #	Structure	LC-MS or MS $(M + H)^+$
3594		635.0
3600		649.8
3701		445.2
3702		493.2

TABLE IIIA-continued

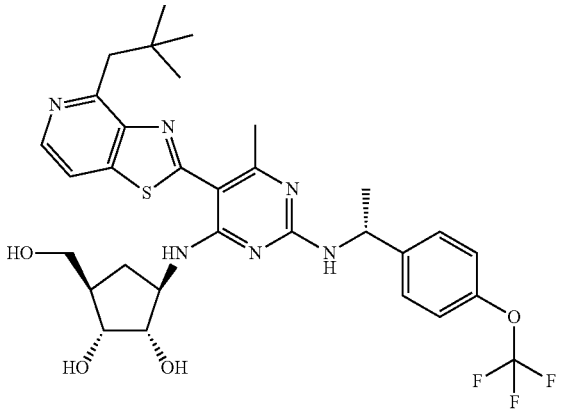
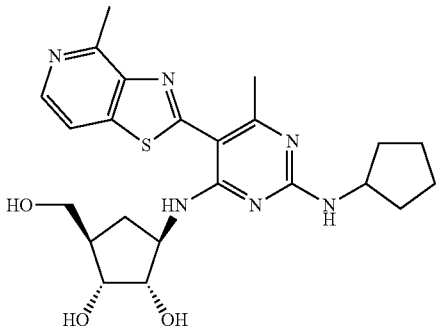
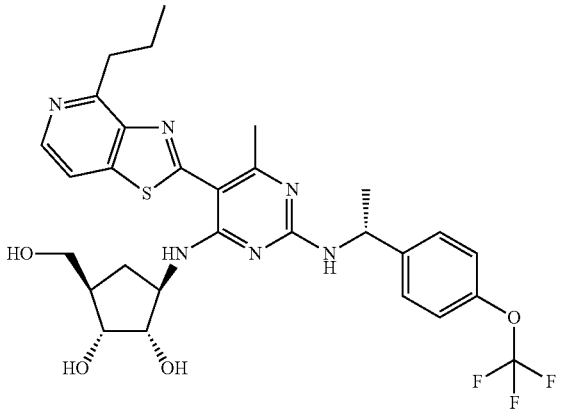
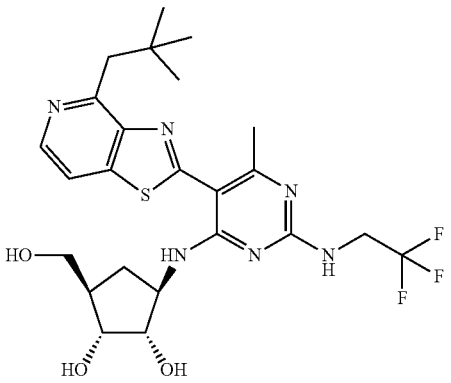
Compd #	Structure	LC-MS or MS $(M + H)^+$
3703		647.2
3704		471.2
3705		619.2
3706		541.2

TABLE IIIA-continued

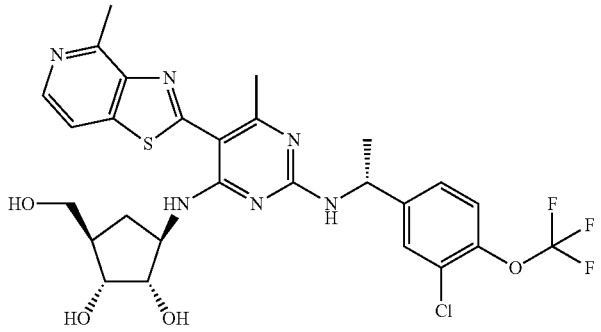
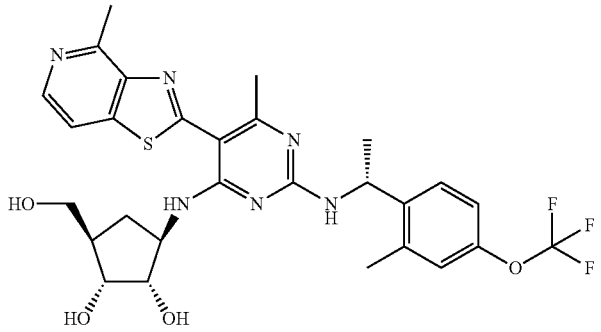
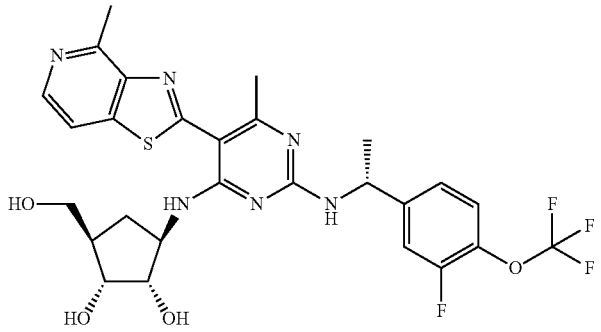
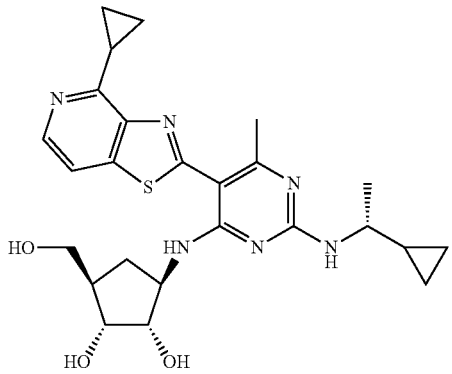
Compd #	Structure	LC-MS or MS $(M + H)^+$
3707		625.30
3708		606.2
3709		609.31
3711		497.2

TABLE IIIA-continued

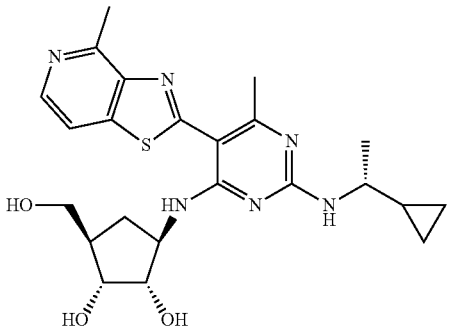
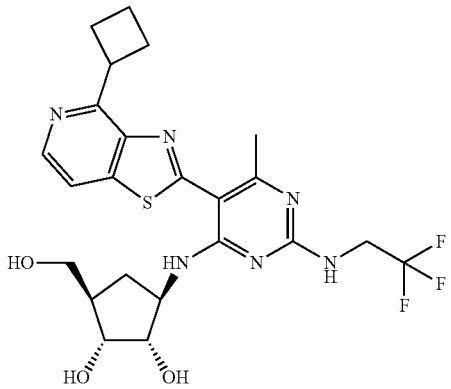
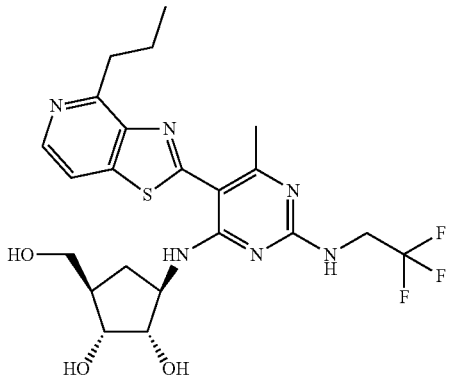
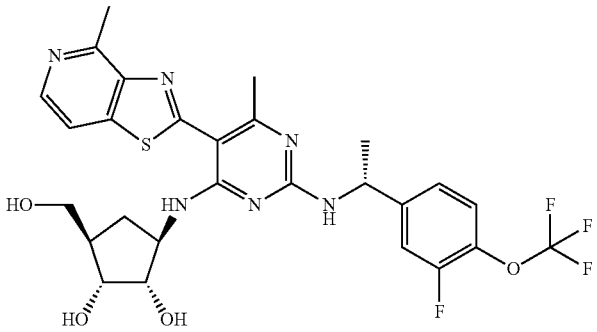
Compd #	Structure	LC-MS or MS $(M + H)^+$
3712		471.2
3714		525.3
3715		513.2
3717		635.3

TABLE IIIA-continued

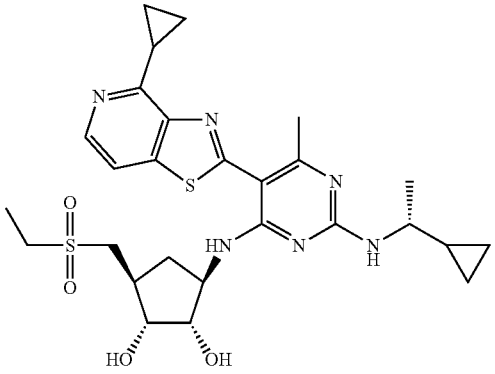
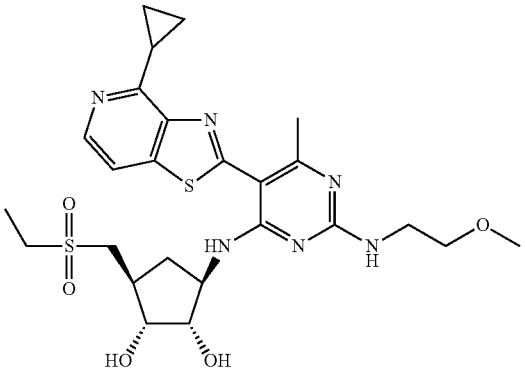
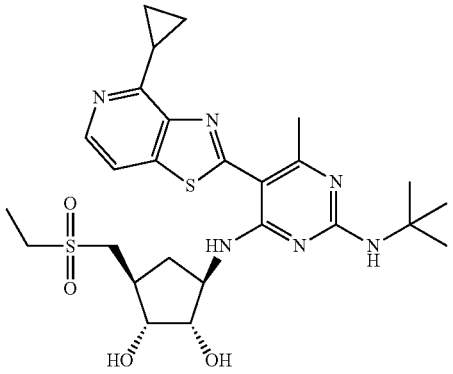
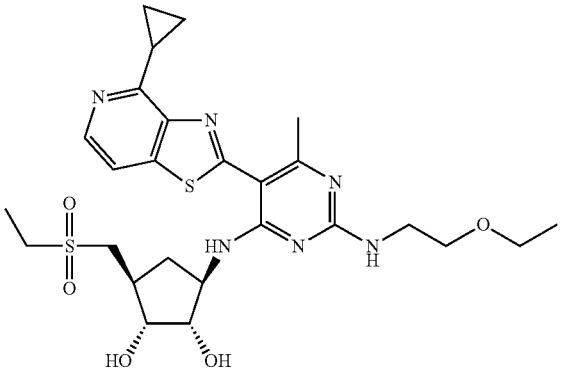
Compd #	Structure	LC-MS or MS $(M + H)^+$
3718		573.4
3719		563.2
3720		561.4
3721		577.2

TABLE IIIA-continued

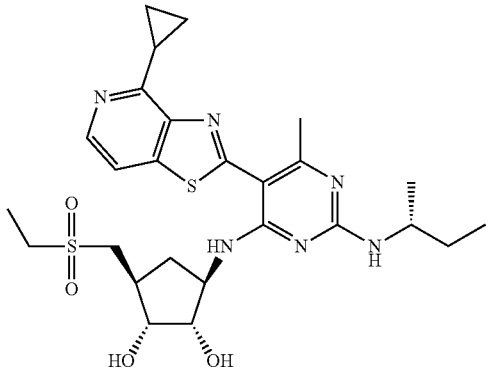
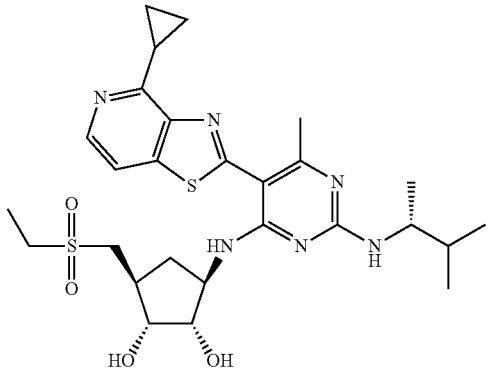
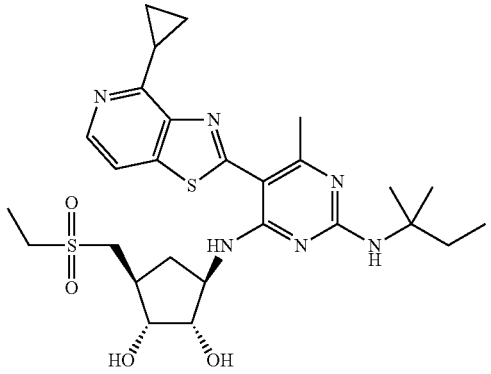
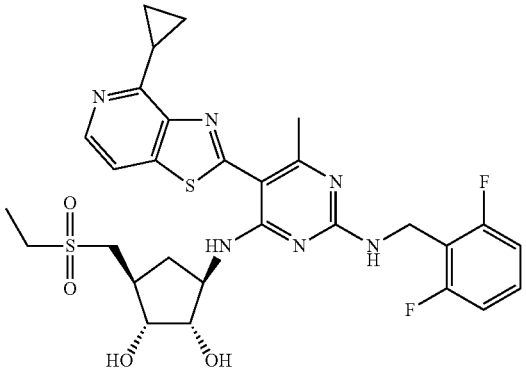
Compd #	Structure	LC-MS or MS $(M + H)^+$
3722		561.2
3723		575.4
3724		575.2
3725		631.41

TABLE IIIA-continued

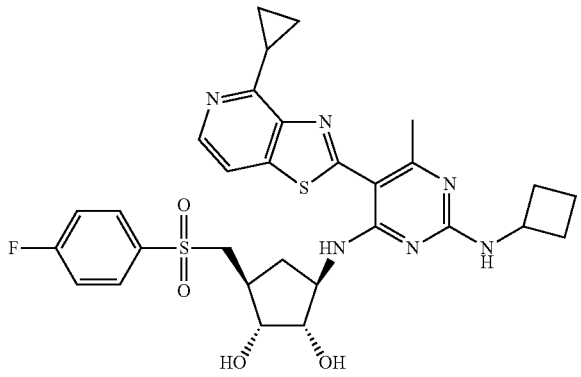
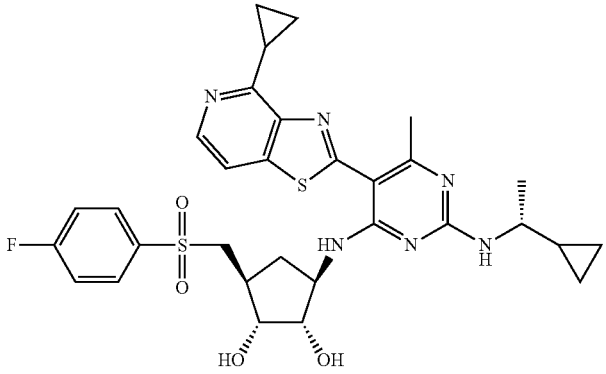
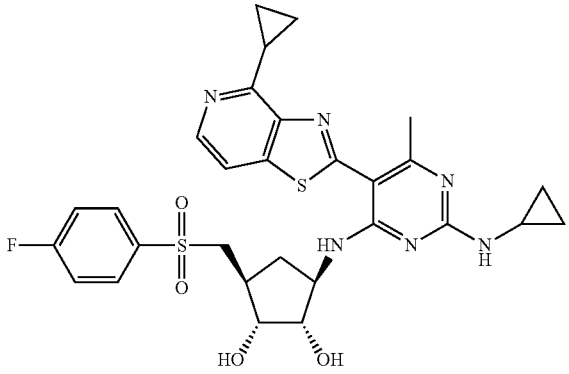
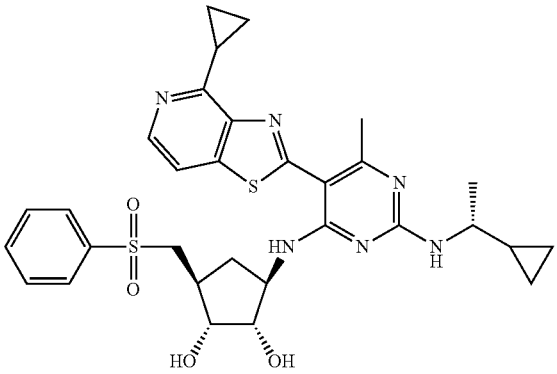
Compd #	Structure	LC-MS or MS $(M + H)^+$
3726		625.2
3727		639.2
3728		611.4
3729		621.4

TABLE IIIA-continued

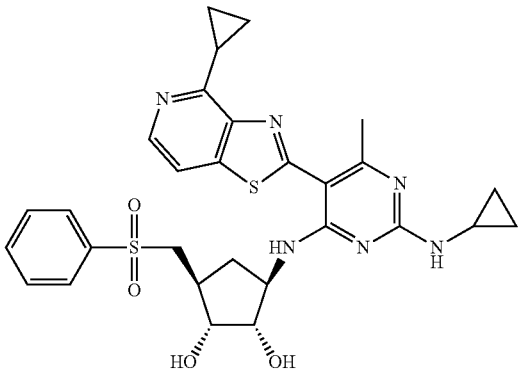
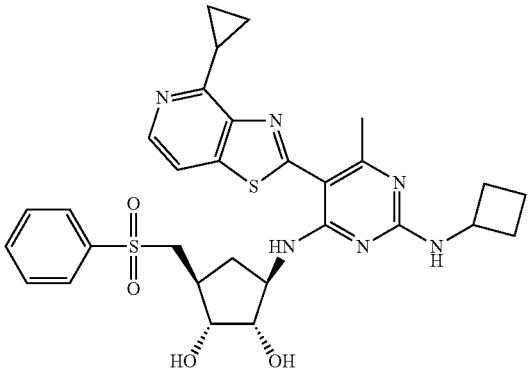
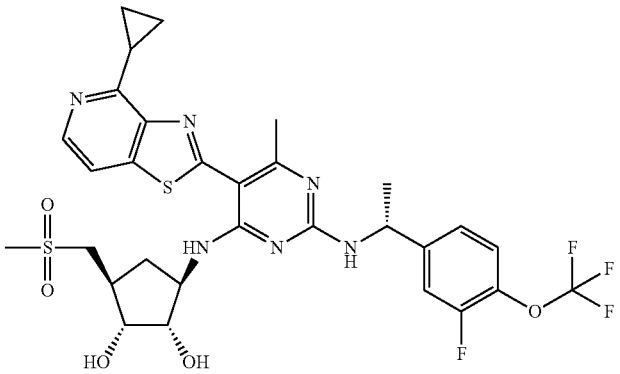
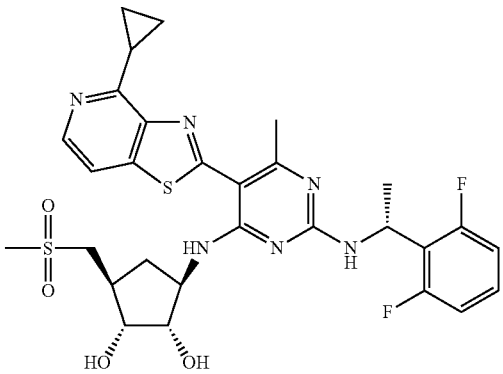
Compd #	Structure	LC-MS or MS $(M + H)^+$
3730		593.4
3731		607.4
3732		697.4
3733		631.4

TABLE IIIA-continued

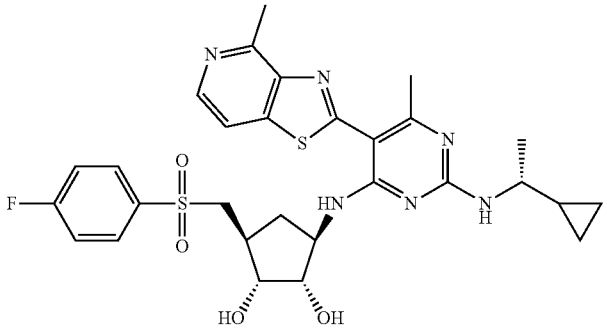
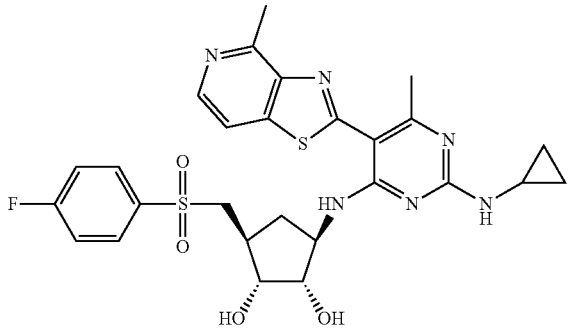
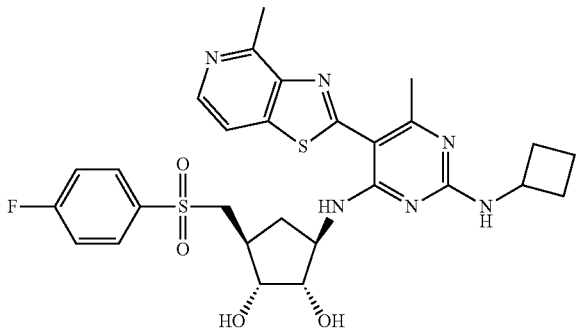
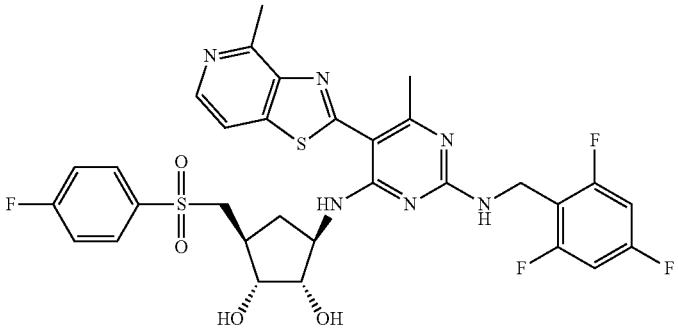
Compd #	Structure	LC-MS or MS $(M + H)^+$
3734		613.3
3735		585.3
3736		599.3
3737		689.3

TABLE IIIA-continued

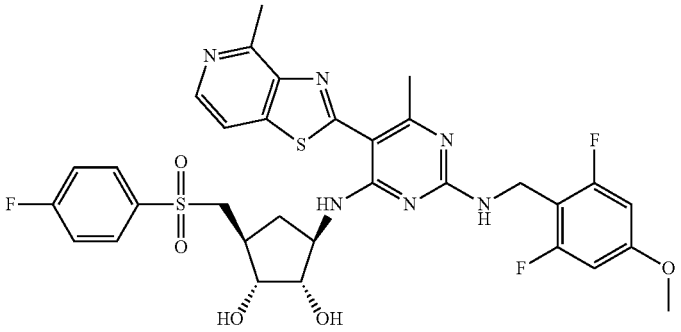
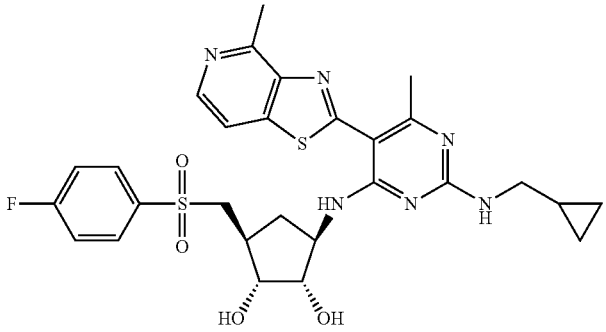
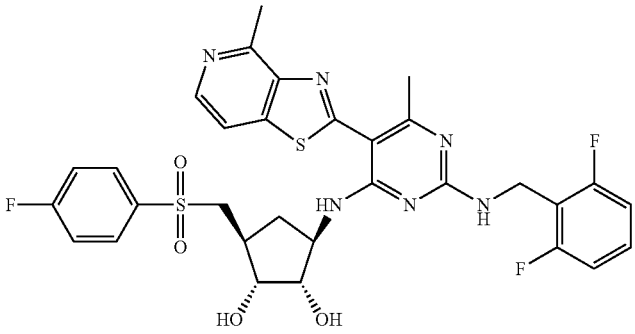
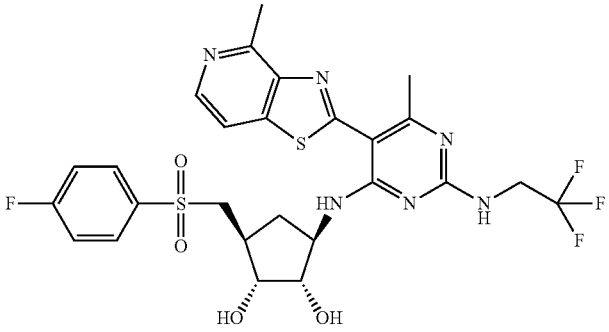
Compd #	Structure	LC-MS or MS $(M + H)^+$
3738		701.4
3739		599.3
3740		671.4
3741		627.3

TABLE IIIA-continued

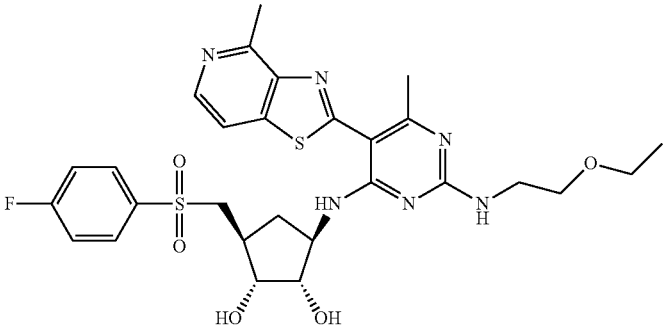
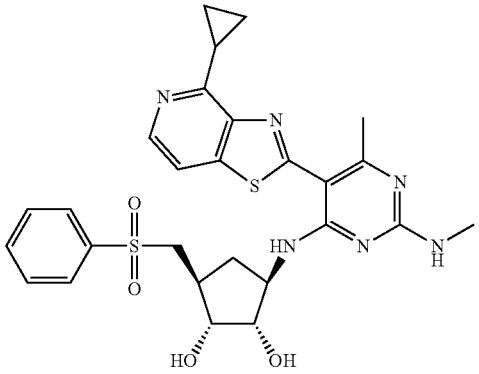
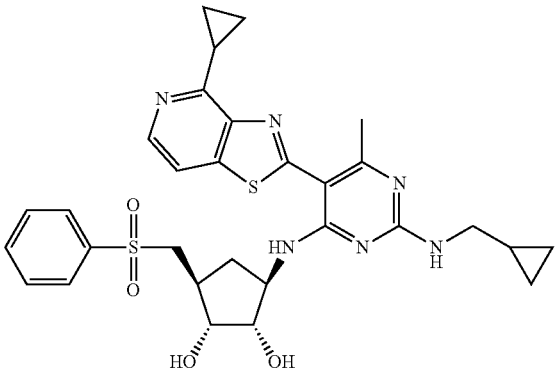
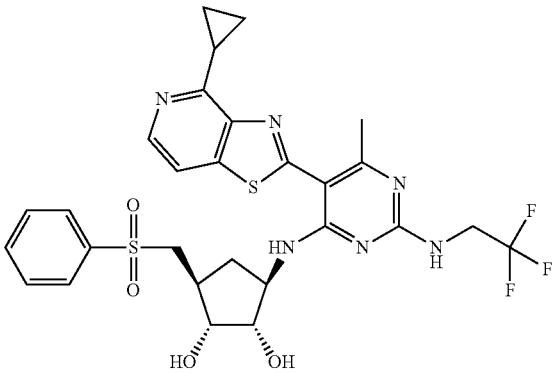
Compd #	Structure	LC-MS or MS $(M + H)^+$
3742		617.4
3743		567.2
3744		607.2
3745		635.0

TABLE IIIA-continued

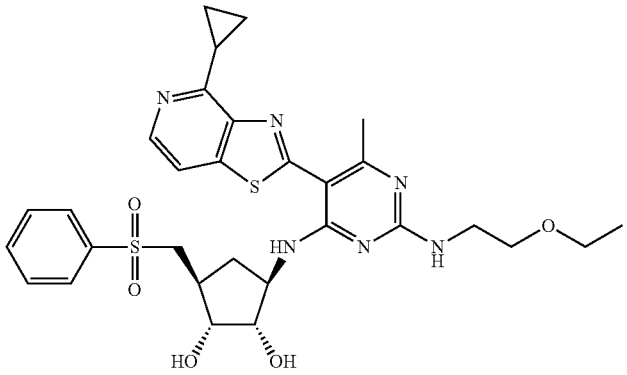
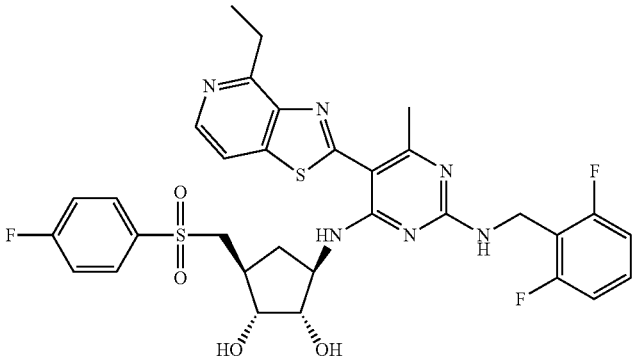
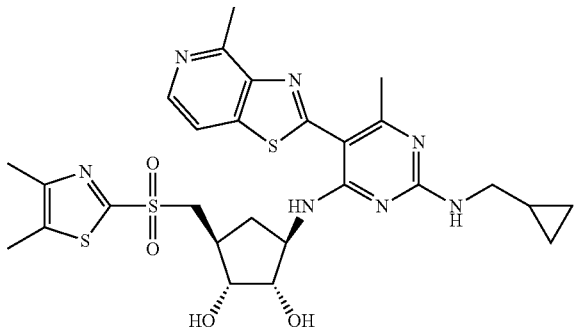
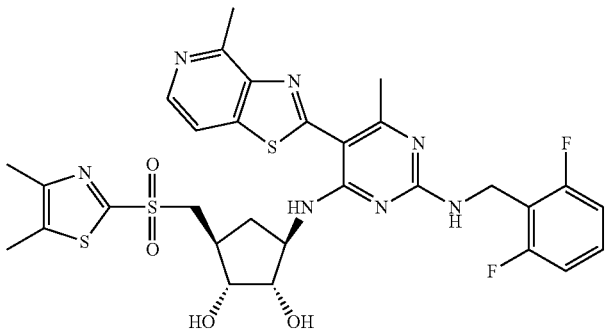
Compd #	Structure	LC-MS or MS $(M + H)^+$
3746		625.2
3747		685.0
3748		616.3
3749		688.3

TABLE IIIA-continued

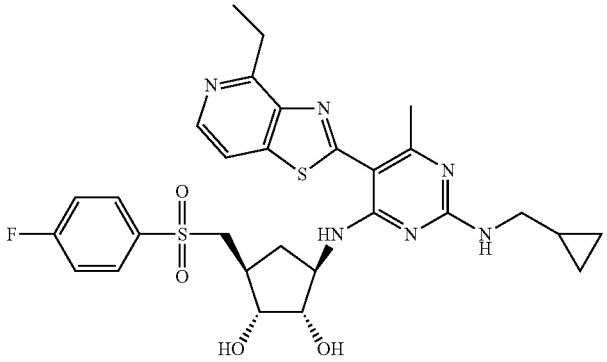
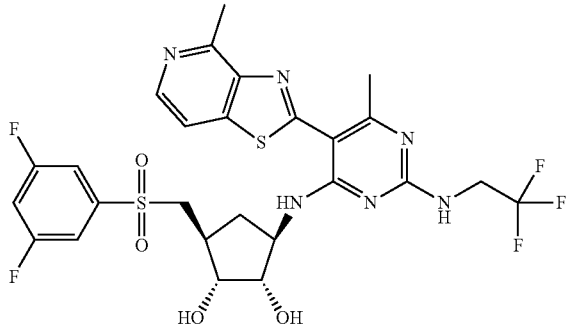
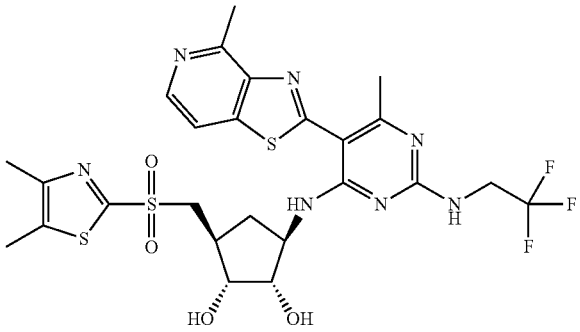
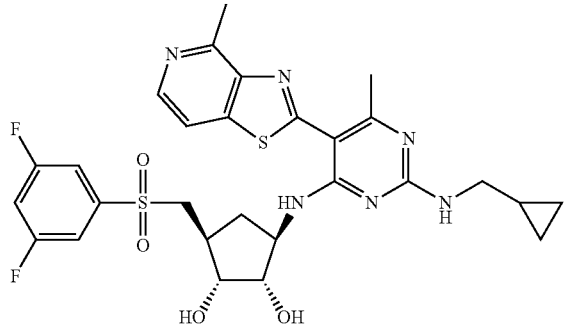
Compd #	Structure	LC-MS or MS $(M + H)^+$
3750		613.3
3751		645.2
3752		644.2
3753		616.0

TABLE IIIA-continued

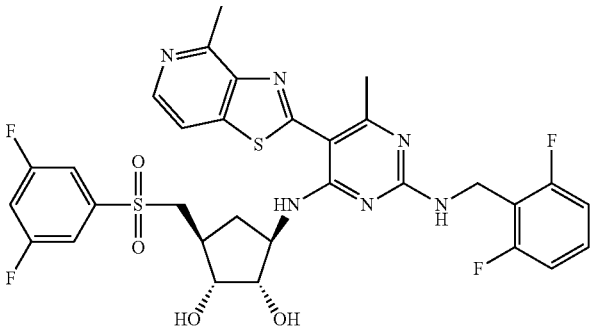
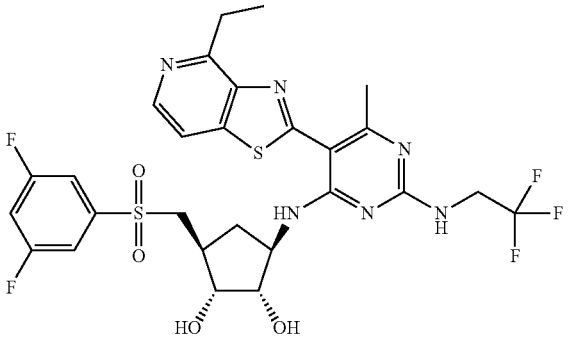
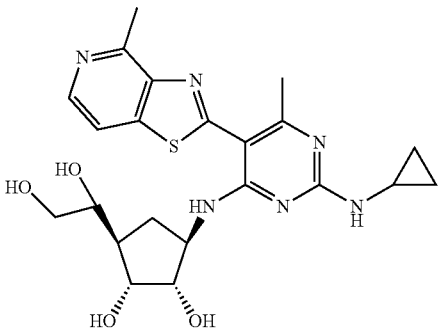
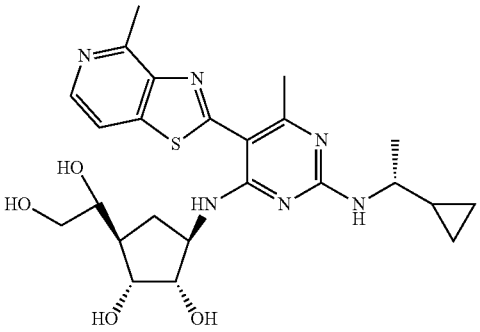
Compd #	Structure	LC-MS or MS $(M + H)^+$
3754		689.30
3755		641.0
3756		473.2
3757		501.4

TABLE IIIA-continued

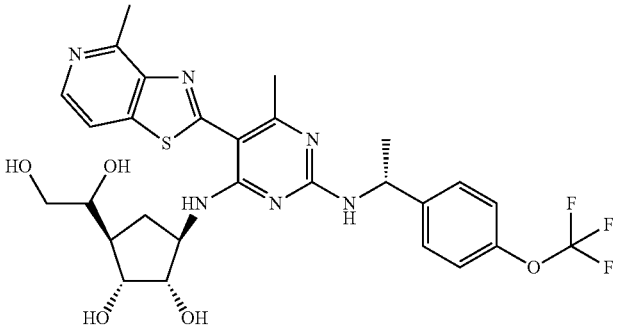
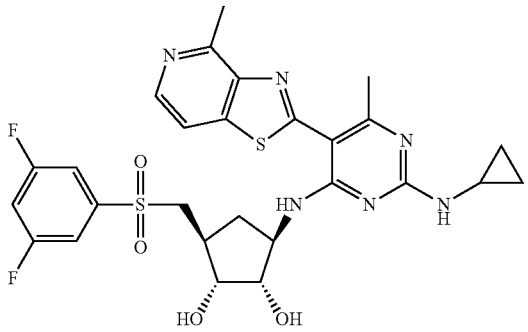
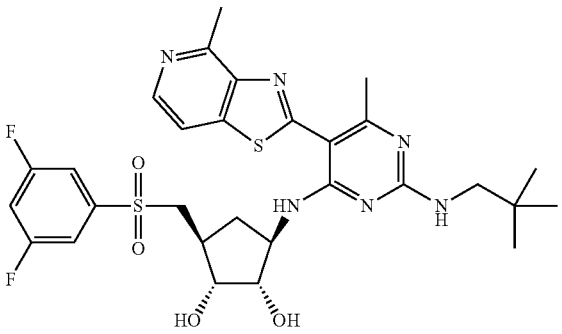
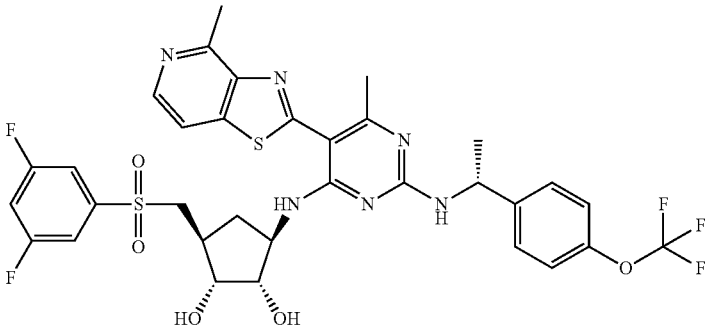
Compd #	Structure	LC-MS or MS $(M + H)^+$
3758		621.2
3759		603.0
3760		633.0
3761		751.5

TABLE IIIA-continued

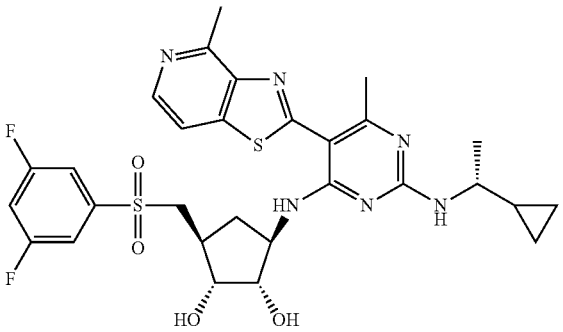
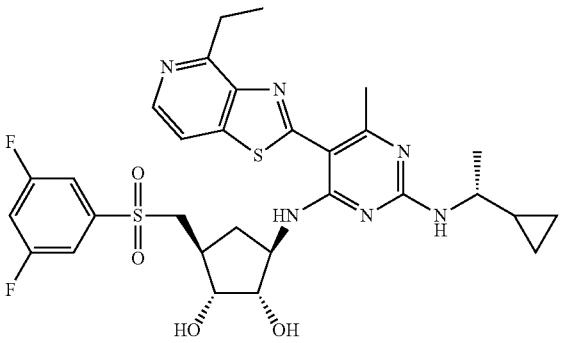
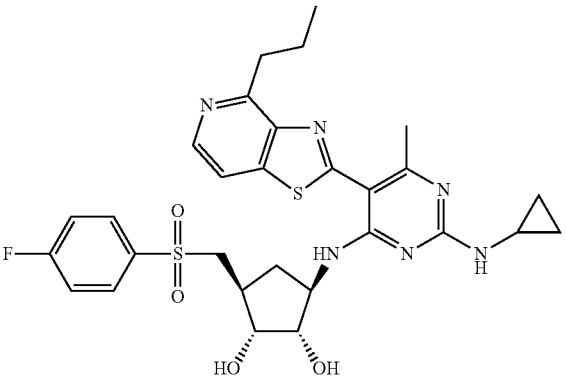
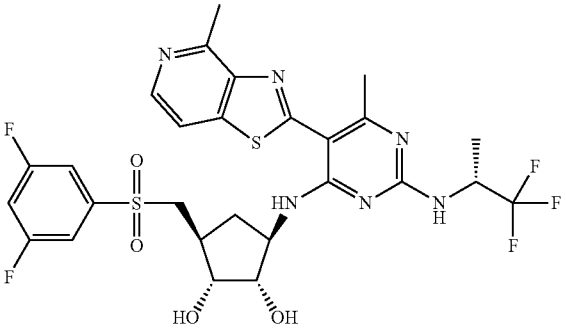
Compd #	Structure	LC-MS or MS $(M + H)^+$
3762		631.5
3763		645.5
3764		613.5
3765		659.5

TABLE IIIA-continued

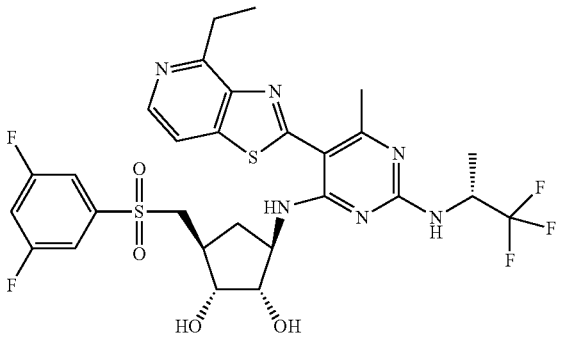
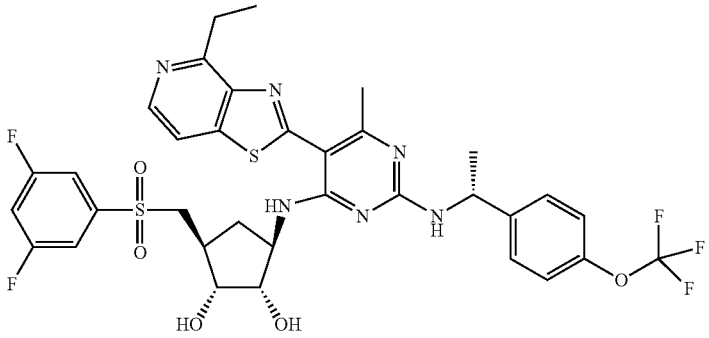
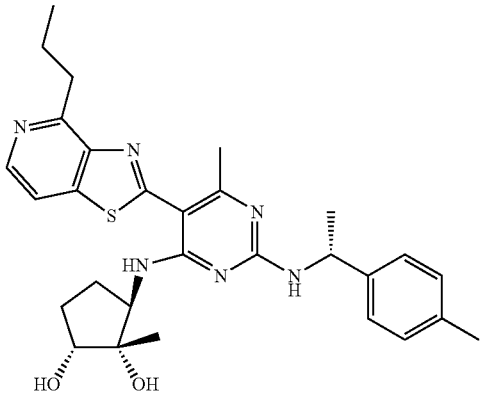
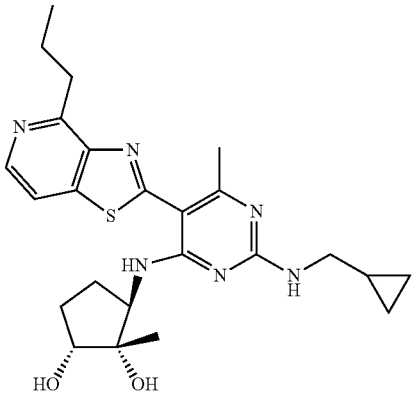
Compd #	Structure	LC-MS or MS $(M + H)^+$
3766		673.5
3767		765.5
3801		533.46
3802		469.42

TABLE IIIA-continued

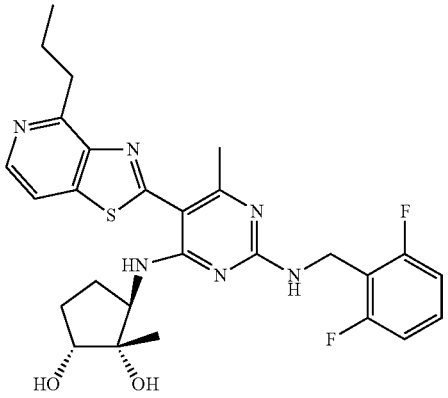
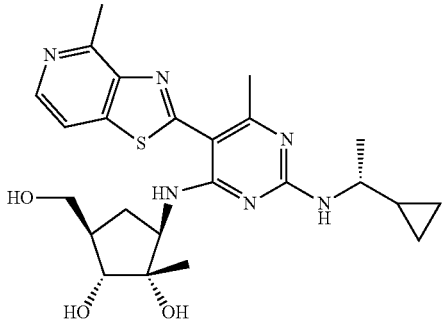
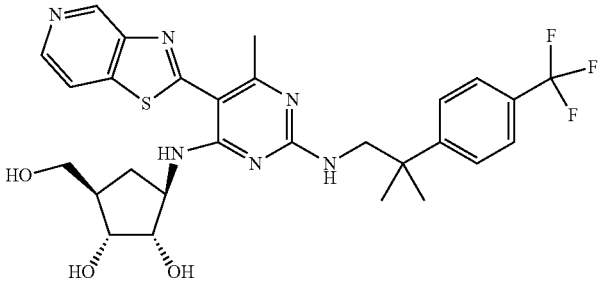
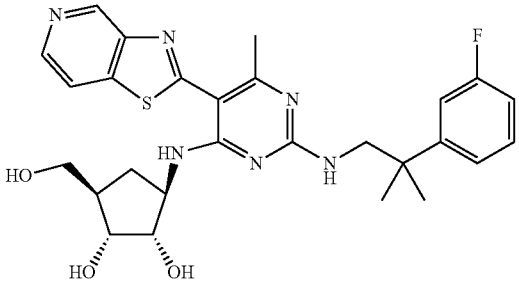
Compd #	Structure	LC-MS or MS $(M + H)^+$
3803		541.39
3804		486.30
3806		589.2
3807		539.2

TABLE IIIA-continued

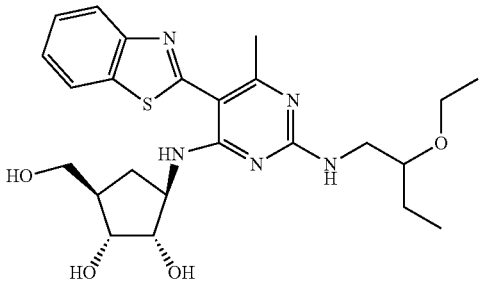
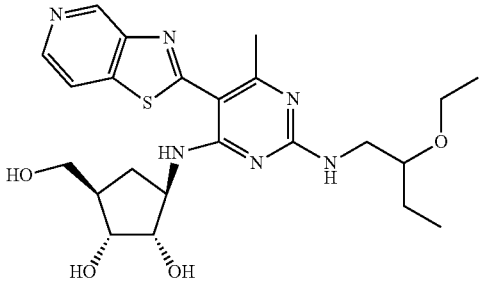
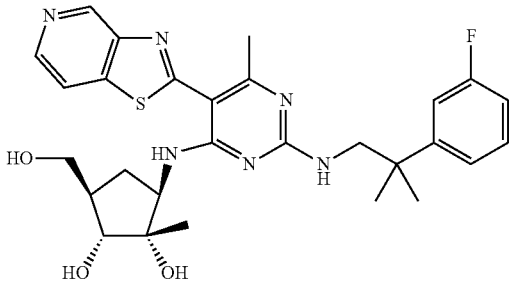
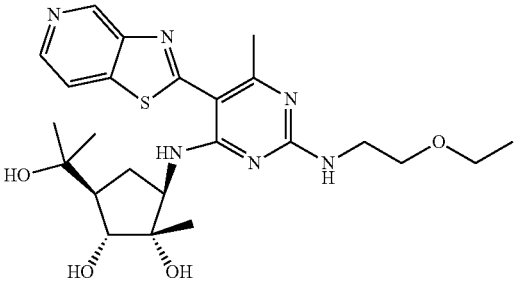
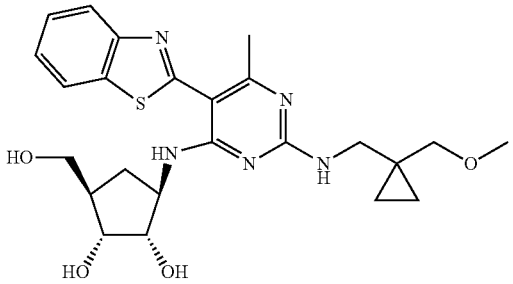
Compd #	Structure	LC-MS or MS $(M + H)^+$
3808		488.2
3809		489.2
3810		575.2 M + Na
3811		503.2
3812		486.2

TABLE IIIA-continued

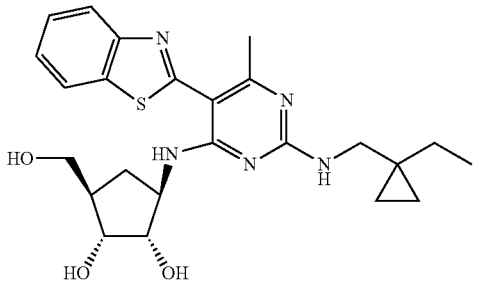
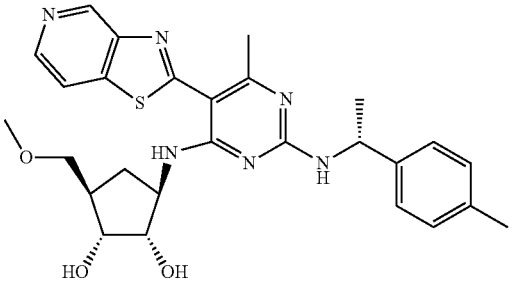
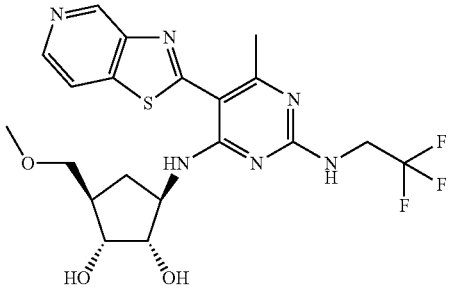
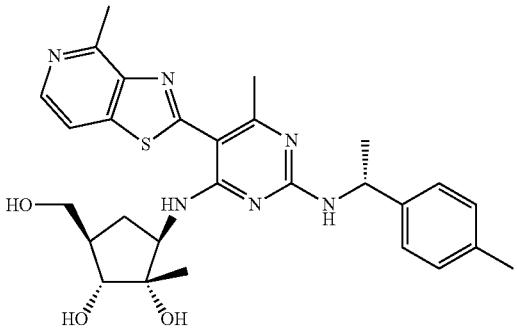
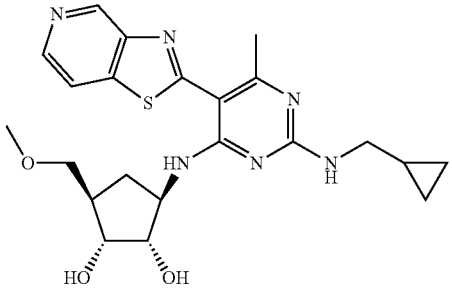
Compd #	Structure	LC-MS or MS $(M + H)^+$
3813		470.2
3814		521.37
3814		485.2
3815		535.30
3815		na

TABLE IIIA-continued

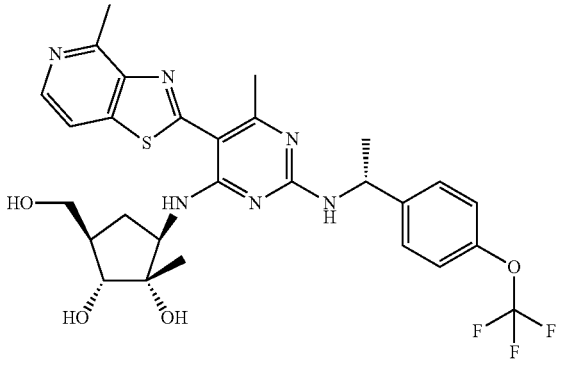
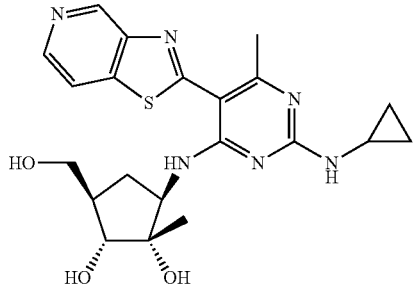
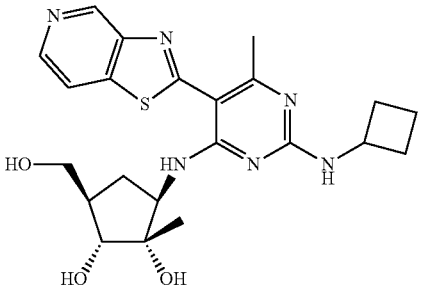
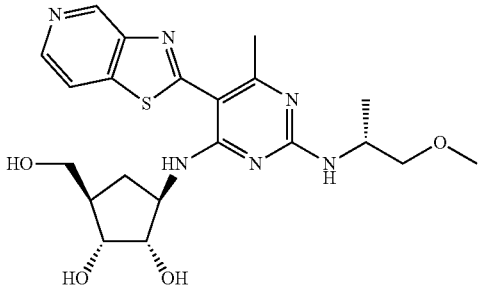
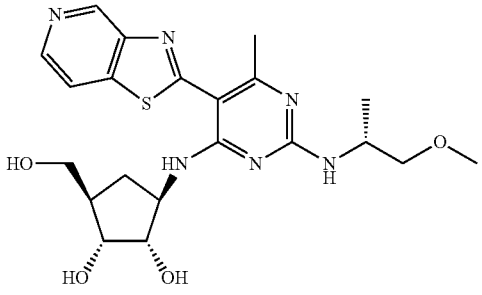
Compd #	Structure	LC-MS or MS $(M + H)^+$
3816		605.2
3817		443.2
3818		457.2
3819		461.2
3820		na

TABLE IIIA-continued

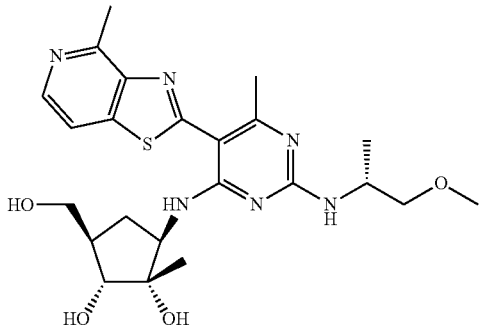
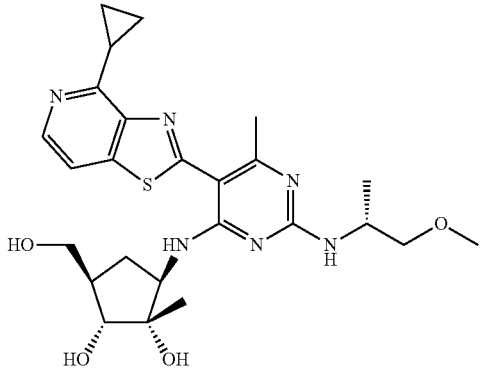
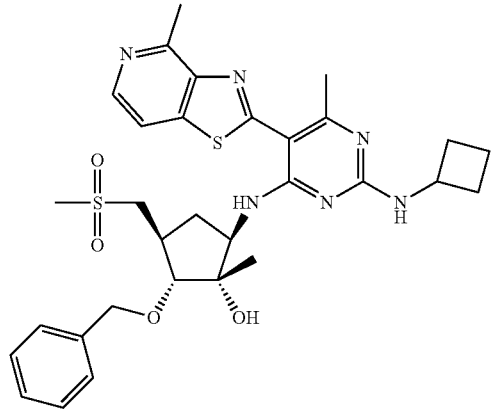
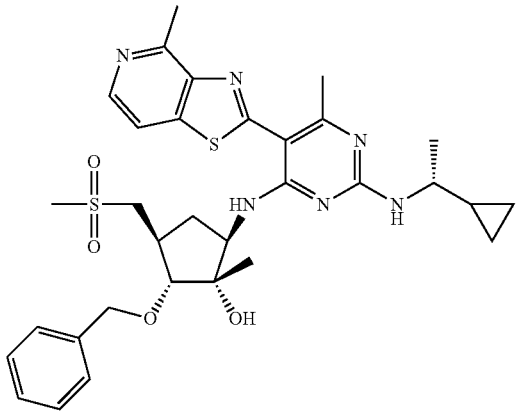
Compd #	Structure	LC-MS or MS $(M + H)^+$
3821		na
3822		501.2
3823		623.2
3824		637.2

TABLE IIIA-continued

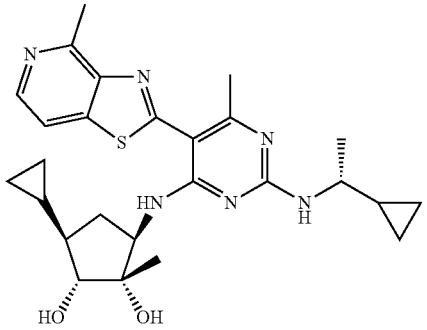
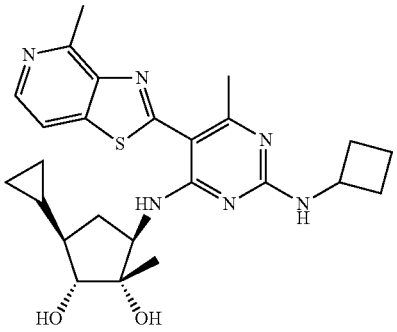
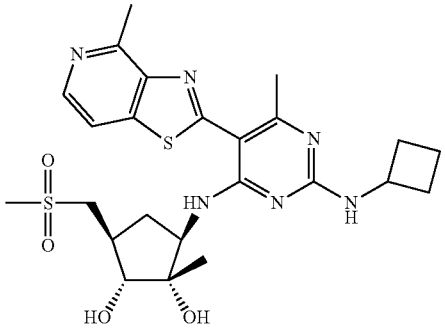
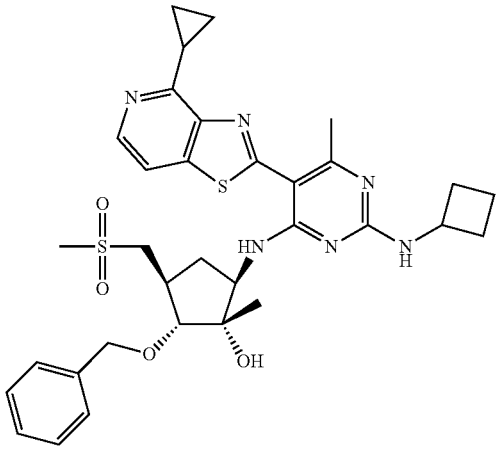
Compd #	Structure	LC-MS or MS $(M + H)^+$
3825		481.2
3826		467.2
3827		533.2
3828		649.2

TABLE IIIA-continued

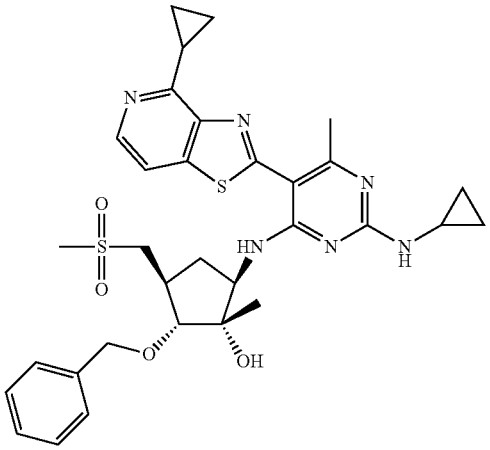
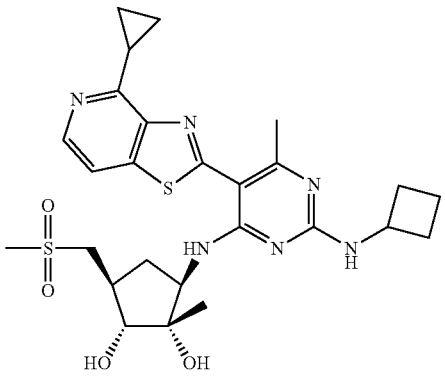
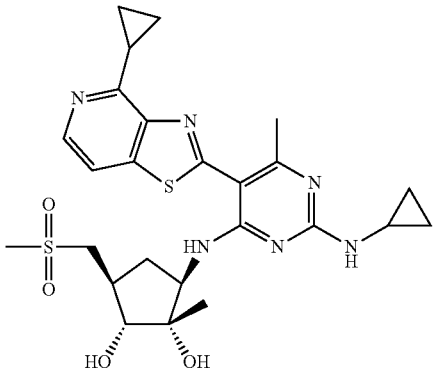
Compd #	Structure	LC-MS or MS $(M + H)^+$
3829		635.2
3830		559.2
3831		546.2

TABLE IIIA-continued

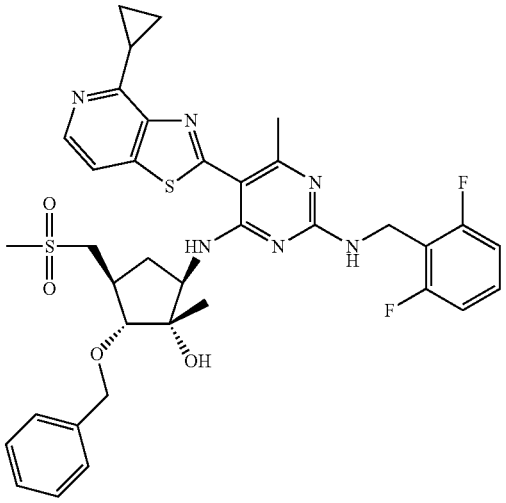
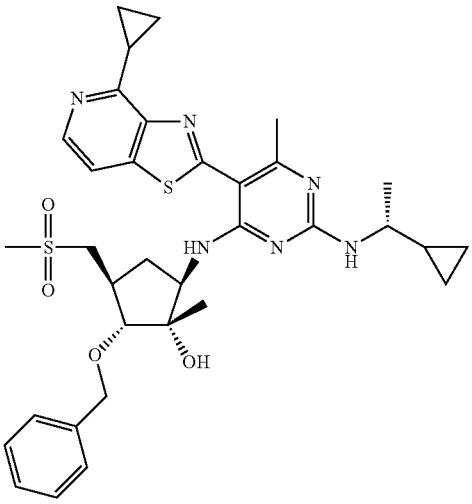
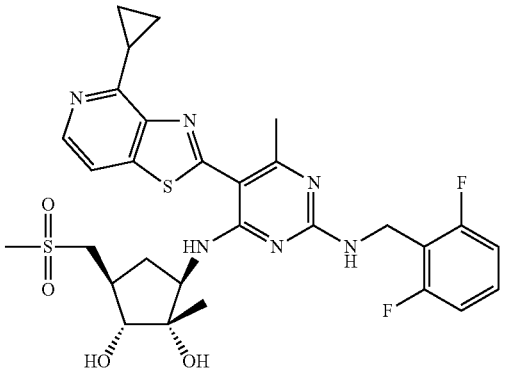
Compd #	Structure	LC-MS or MS $(M + H)^+$
3832		721.0
3833		663.2
3834		631.1

TABLE IIIA-continued

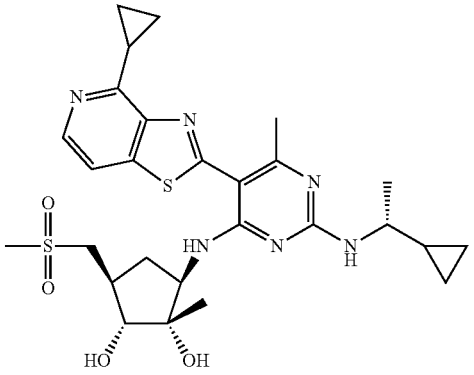
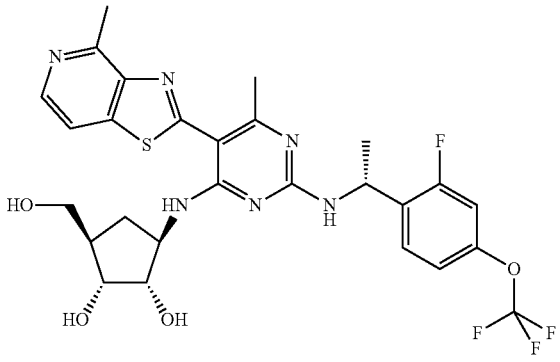
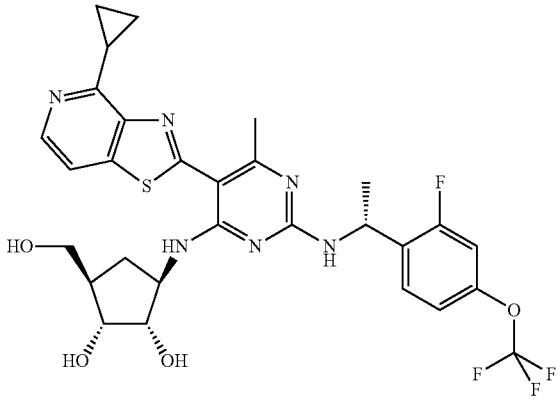
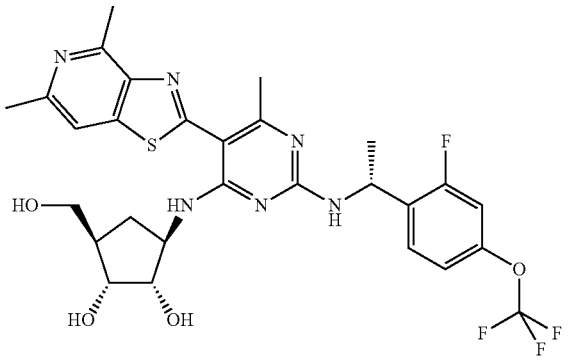
Compd #	Structure	LC-MS or MS $(M + H)^+$
3835		573.2
3836		609.2
3837		635.2
3838		623.2

TABLE IIIA-continued

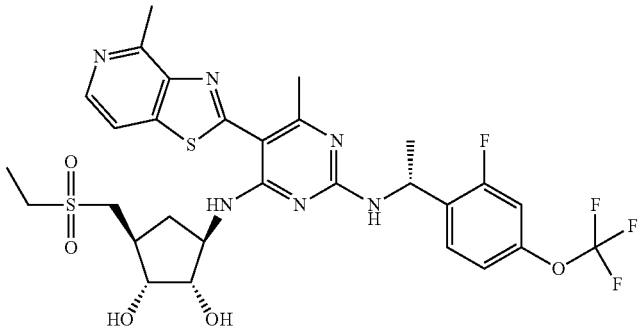
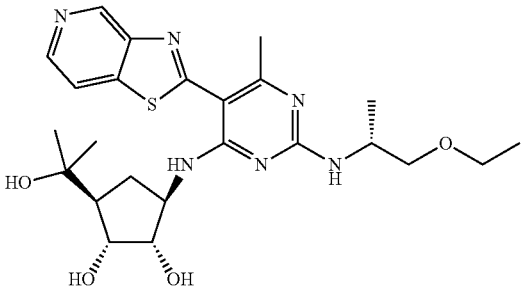
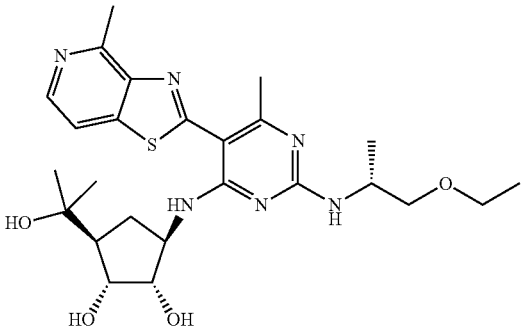
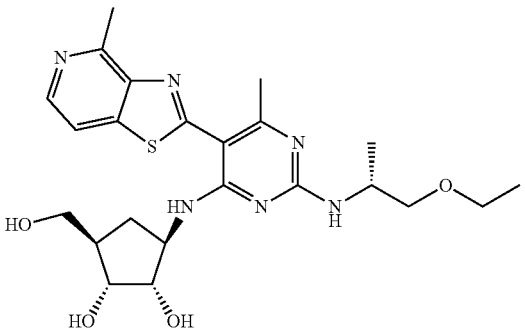
Compd #	Structure	LC-MS or MS $(M + H)^+$
3840		685.0
3841		503.2
3842		517.2
3843		na

TABLE IIIA-continued

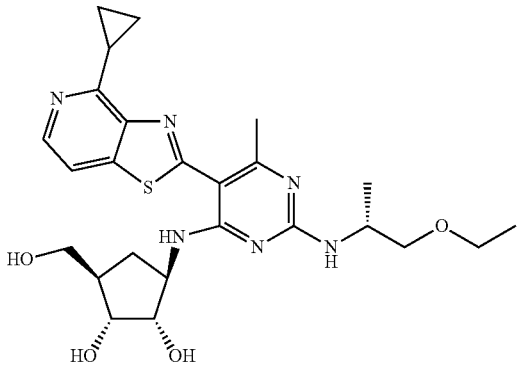
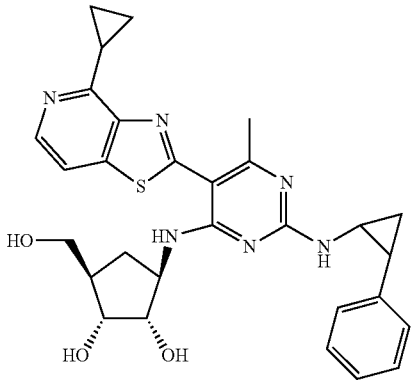
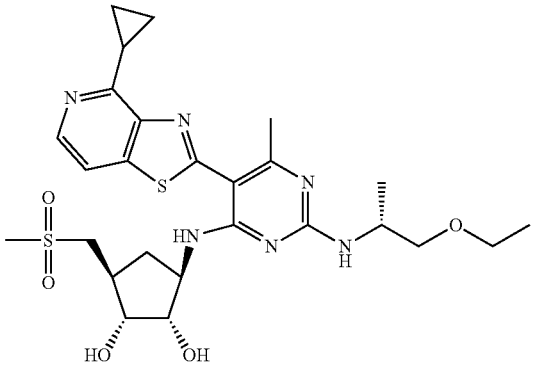
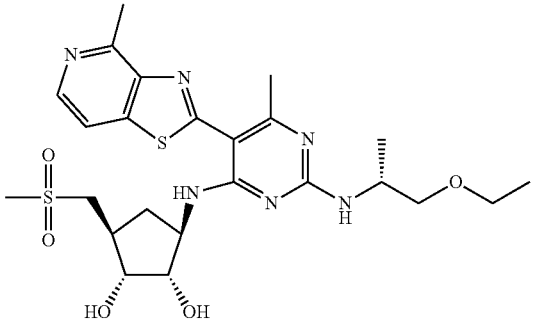
Compd #	Structure	LC-MS or MS $(M + H)^+$
3844		515.2
3845		545.2
3846		577.2
3847		551.2

TABLE IIIA-continued

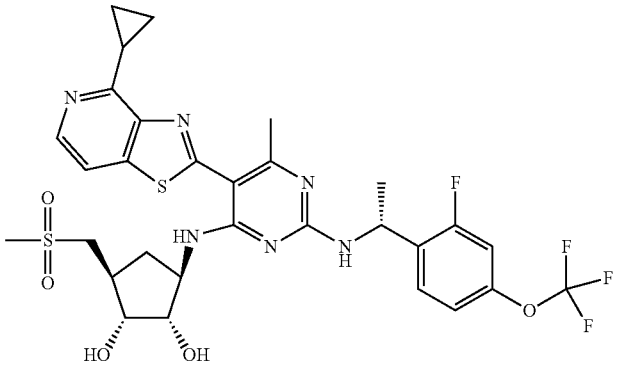
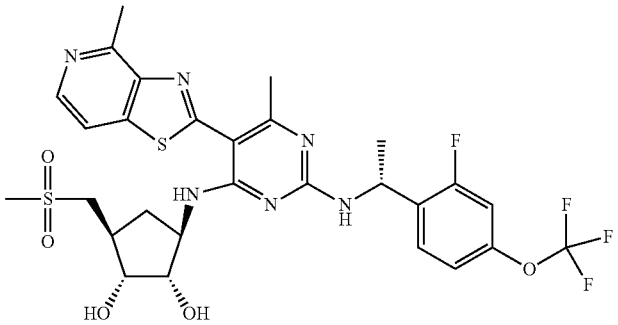
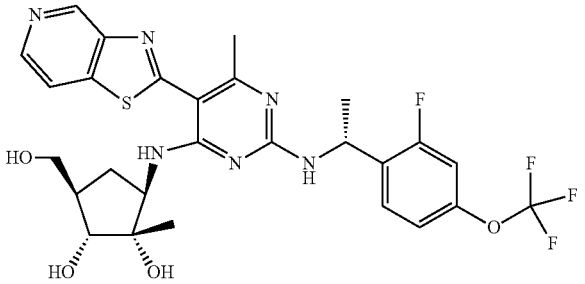
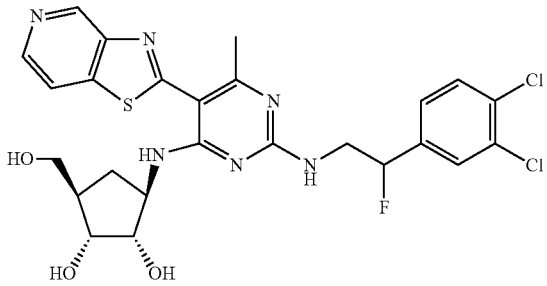
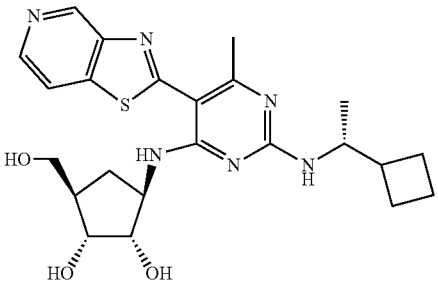
Compd #	Structure	LC-MS or MS $(M + H)^+$
3848		697.0
3849		671.0
3850		608.8
3901		579
3903		471

TABLE IIIA-continued

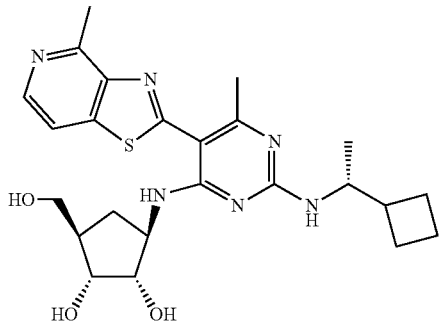
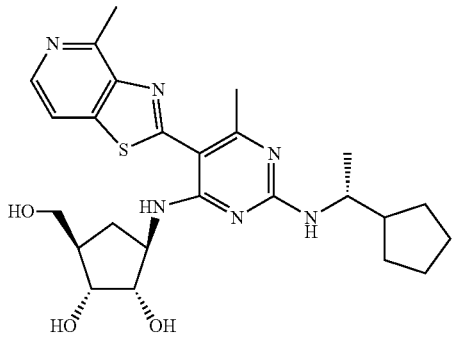
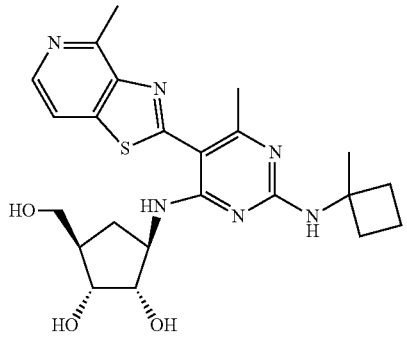
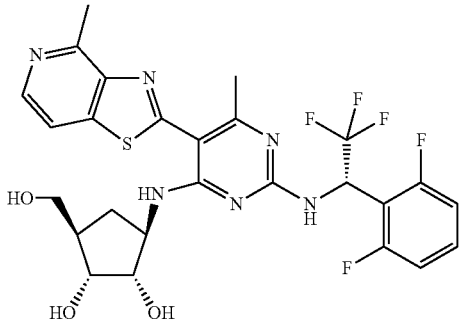
Compd #	Structure	LC-MS or MS $(M + H)^+$
3904		485
3905		499
3906		471
3907		—

TABLE IIIA-continued

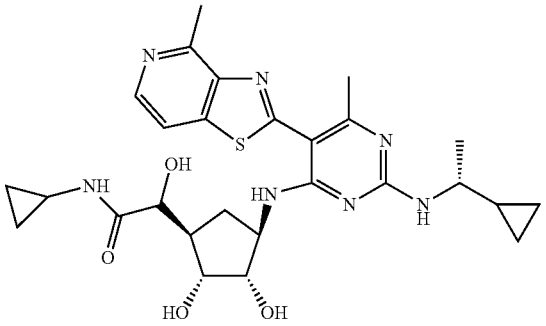
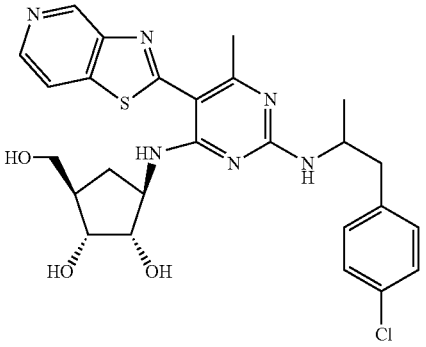
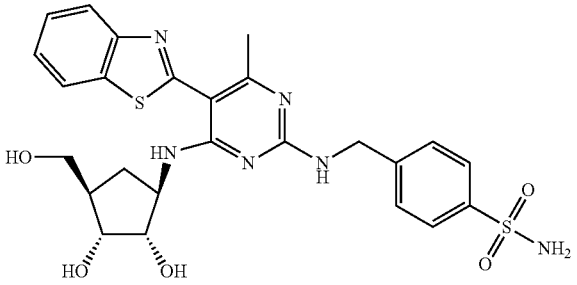
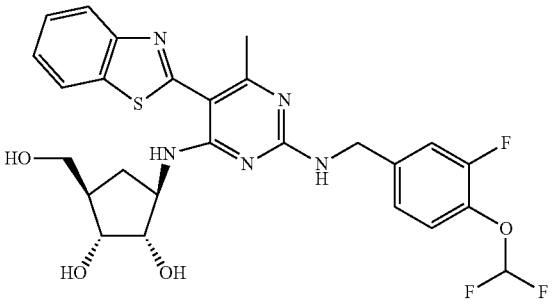
Compd #	Structure	LC-MS or MS $(M + H)^+$
3908		554
4001		541
4002		557
4003		562

TABLE IIIA-continued

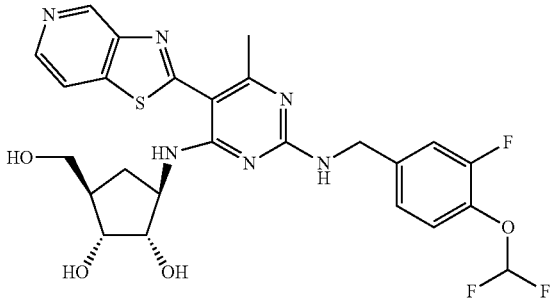
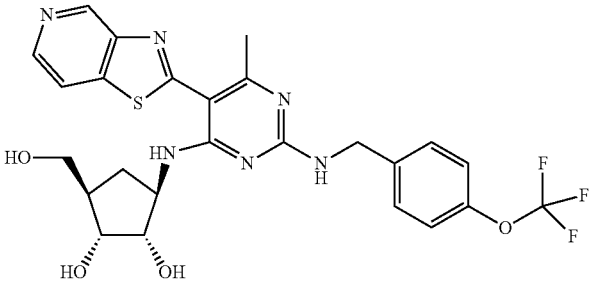
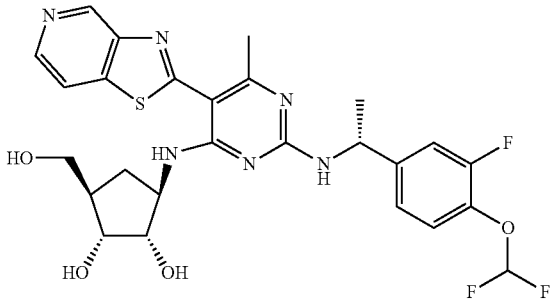
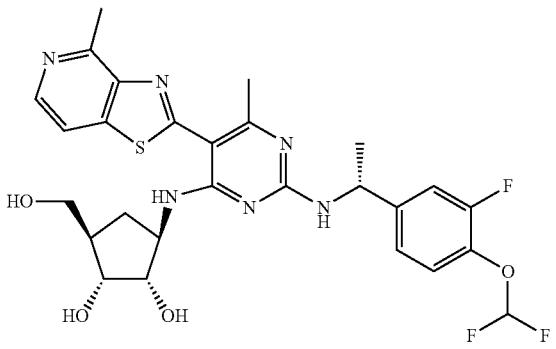
Compd #	Structure	LC-MS or MS $(M + H)^+$
4004		563
4006		563
4007		577
4008		591

TABLE IIIA-continued

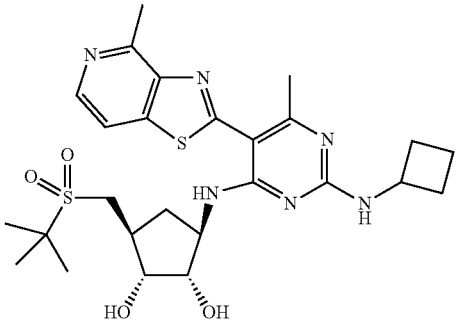
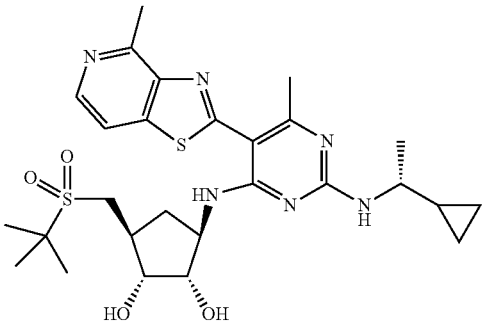
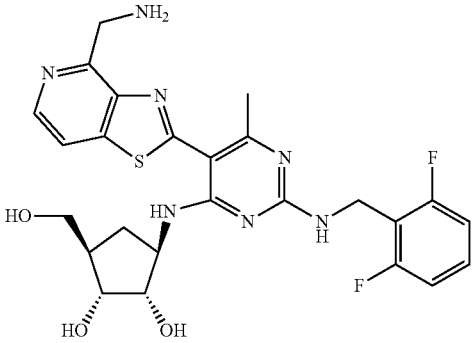
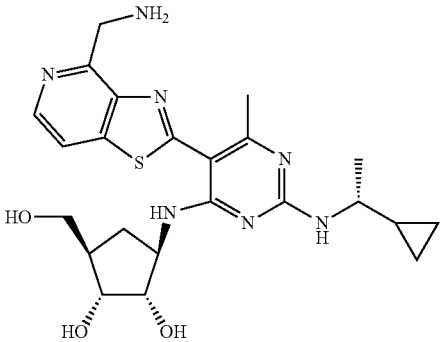
Compd #	Structure	LC-MS or MS $(M + H)^+$
4009		561
4010		575
4012		544
4013		486

TABLE IIIA-continued

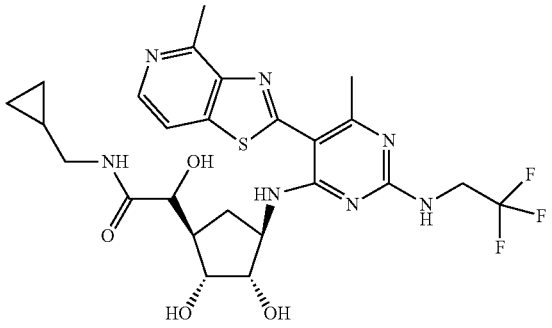
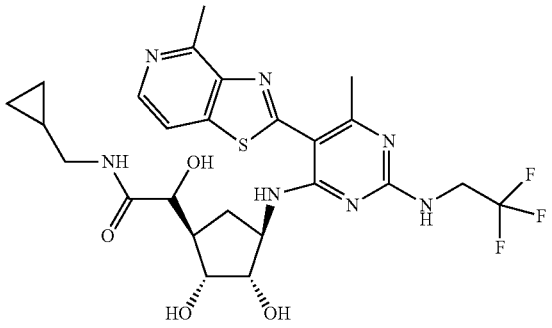
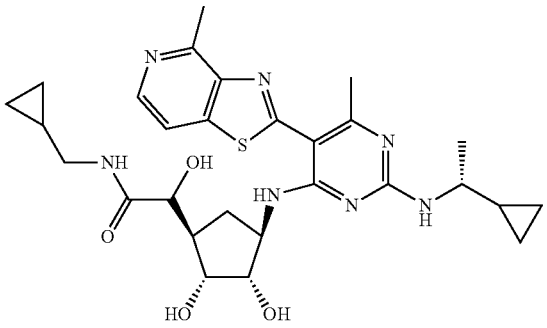
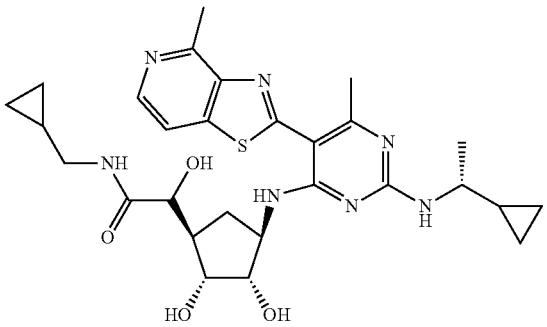
Compd #	Structure	LC-MS or MS $(M + H)^+$
4014		582
4015		582
4016		568
4017		568

TABLE IIIA-continued

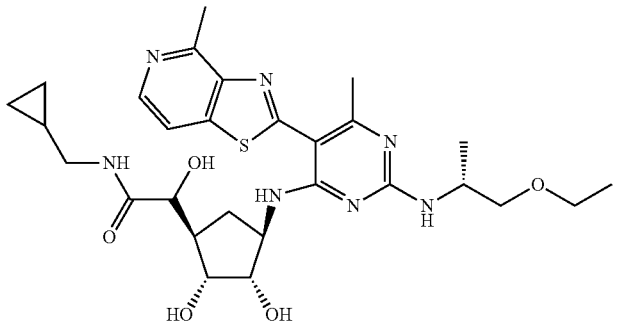
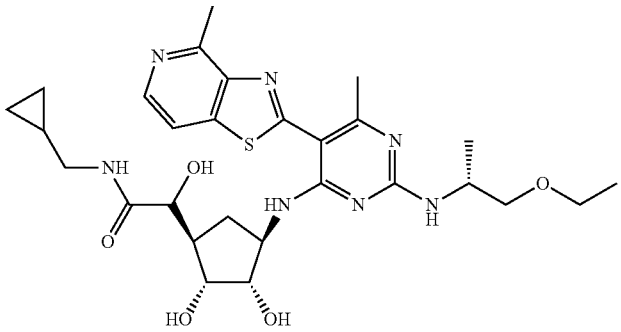
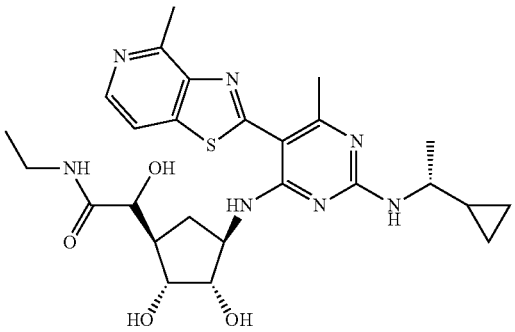
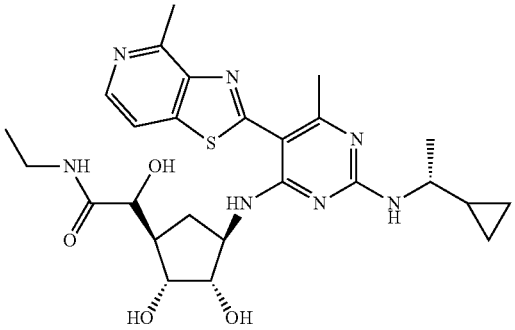
Compd #	Structure	LC-MS or MS $(M + H)^+$
4018		586
4019		586
4020		542
4021		542

TABLE IIIA-continued

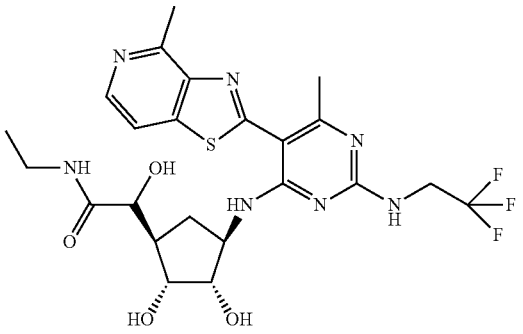
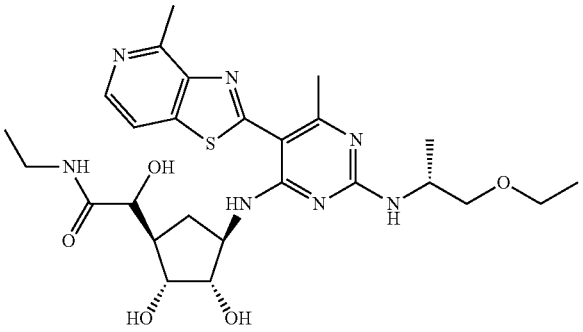
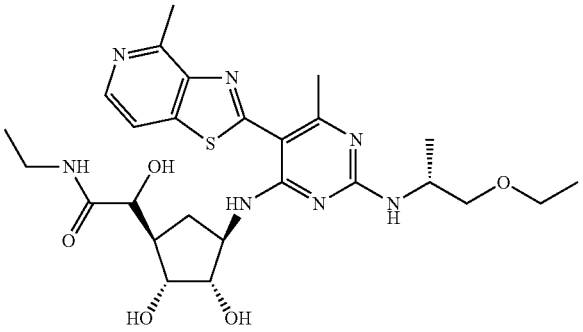
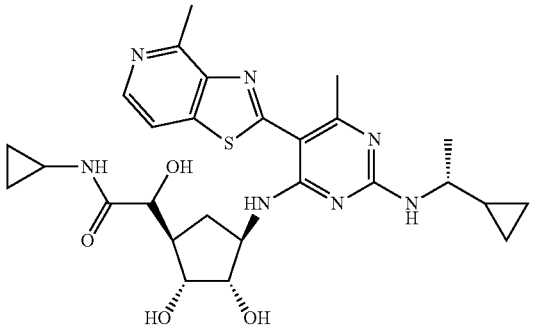
Compd #	Structure	LC-MS or MS $(M + H)^+$
4023		556
4024		560
4025		560
4026		554

TABLE IIIA-continued

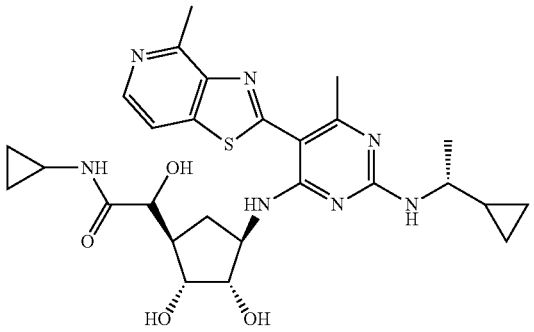
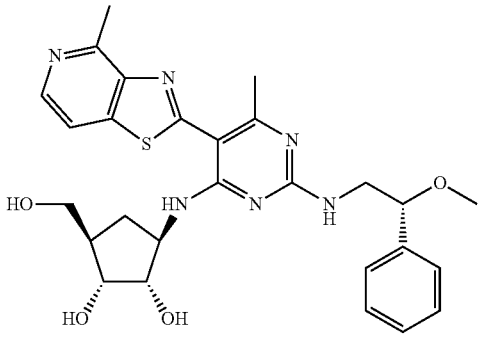
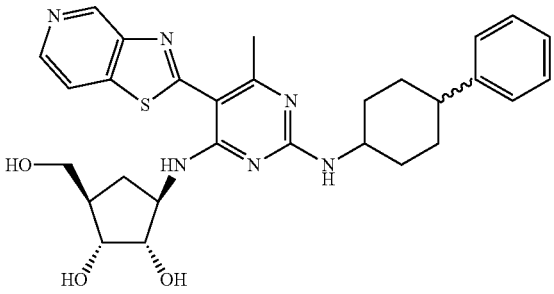
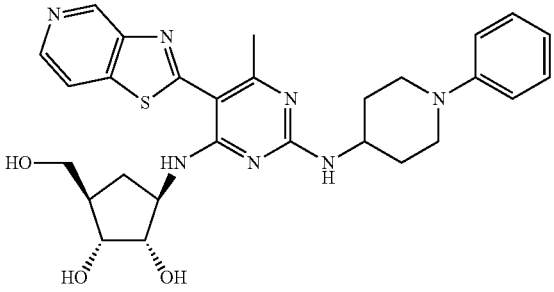
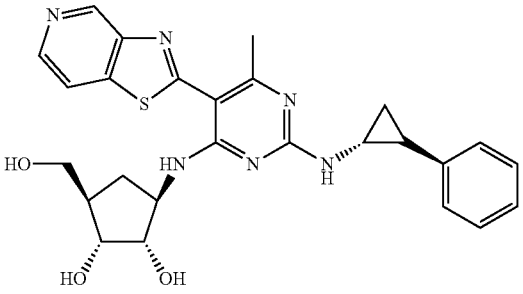
Compd #	Structure	LC-MS or MS $(M + H)^+$
4027		554
4028		537
4105		547.3
4106		548.3
4107		505.3

TABLE IIIA-continued

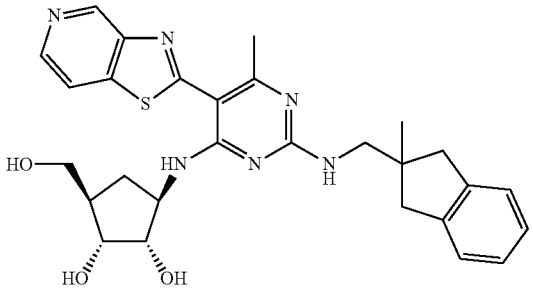
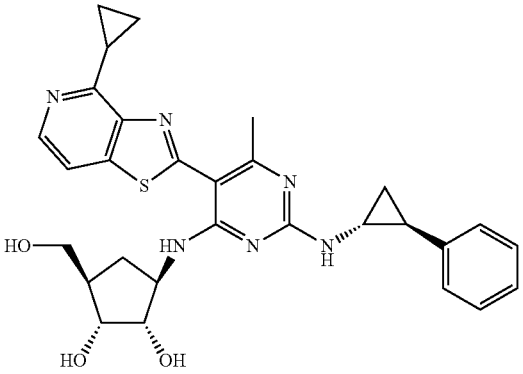
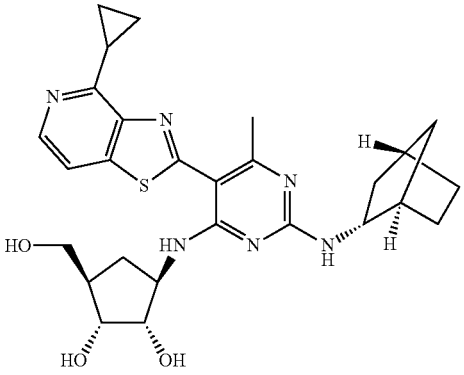
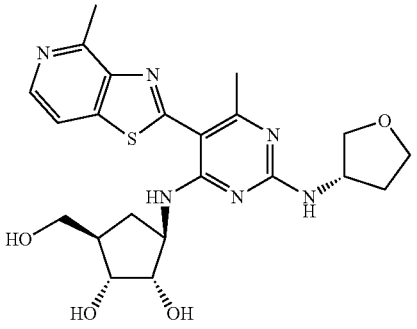
Compd #	Structure	LC-MS or MS $(M + H)^+$
4109		533.3
4114		545.3
4115		523.3
4116		473.3

TABLE IIIA-continued

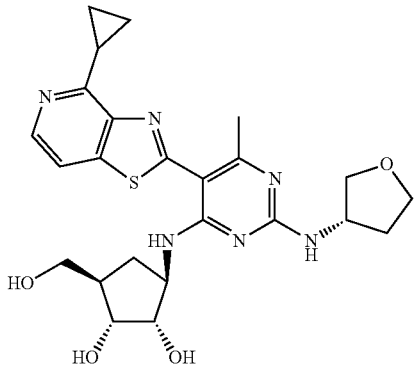
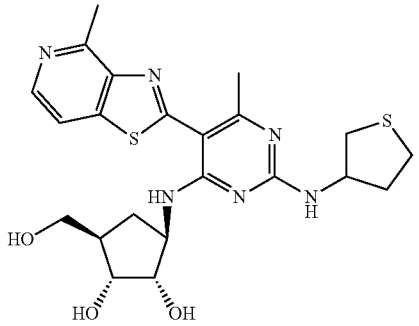
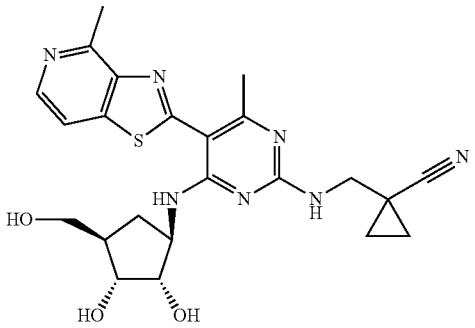
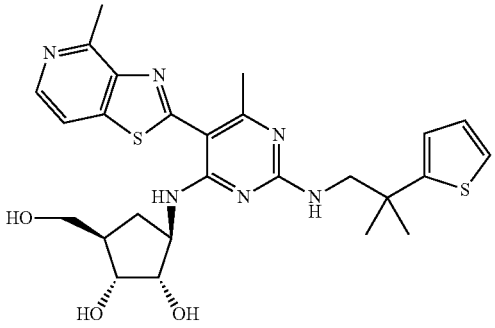
Compd #	Structure	LC-MS or MS $(M + H)^+$
4117		499.3
4119		489.3
4120		482.3
4121		541.3

TABLE IIIA-continued

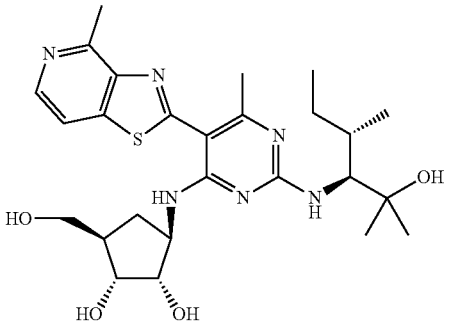
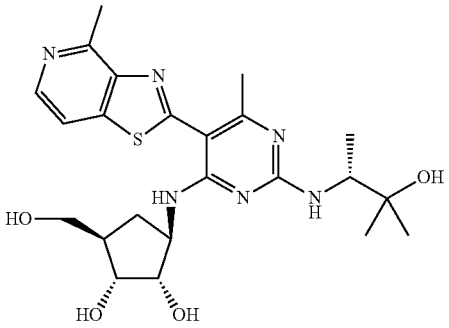
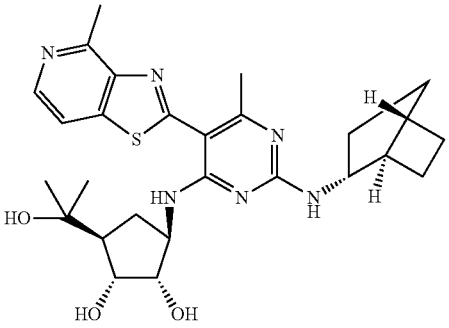
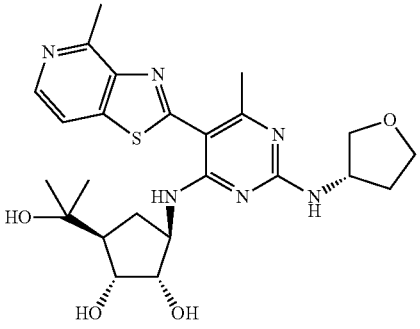
Compd #	Structure	LC-MS or MS $(M + H)^+$
4122		531.3
4123		489.3
4125		525.3
4126		501.3

TABLE IIIA-continued

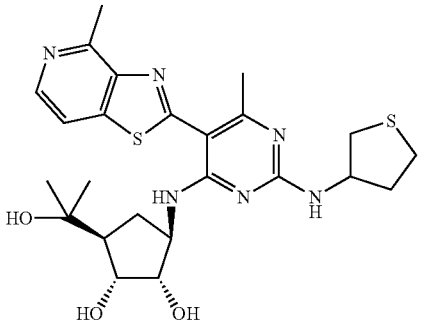
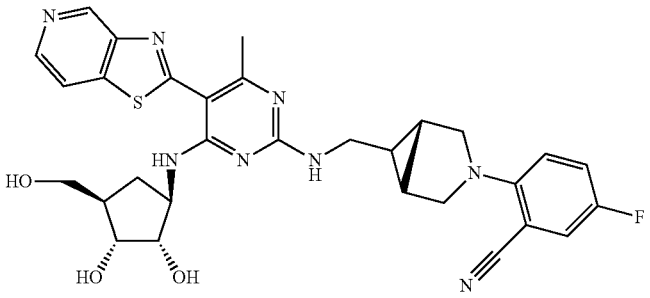
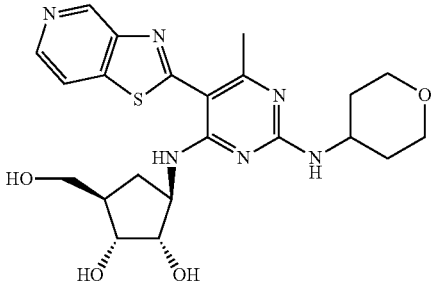
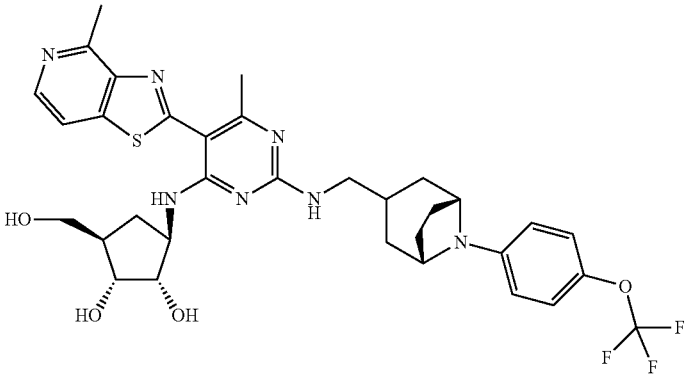
Compd #	Structure	LC-MS or MS $(M + H)^+$
4127		517.3
4203		603.3
4204		473.3
4205		686.4

TABLE IIIA-continued

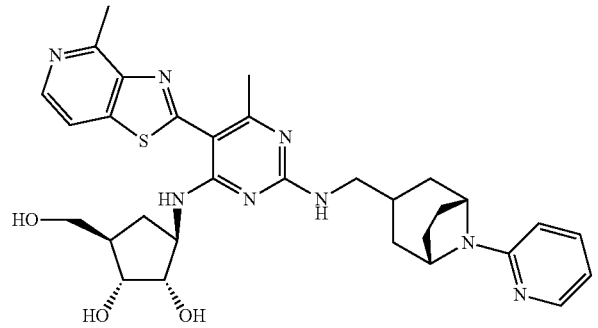
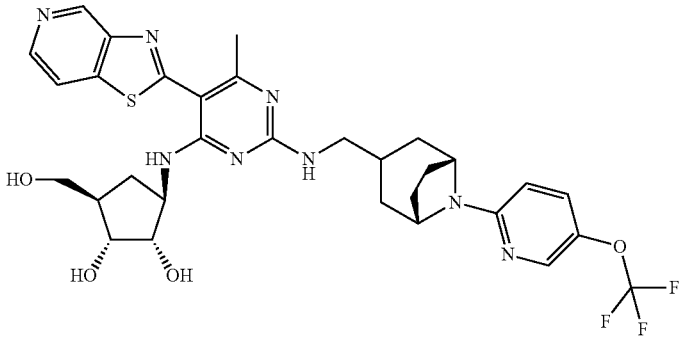
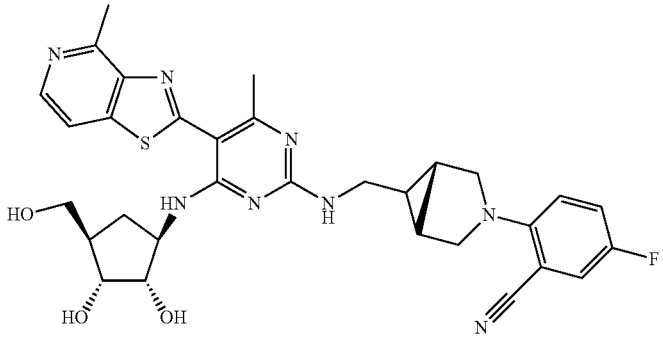
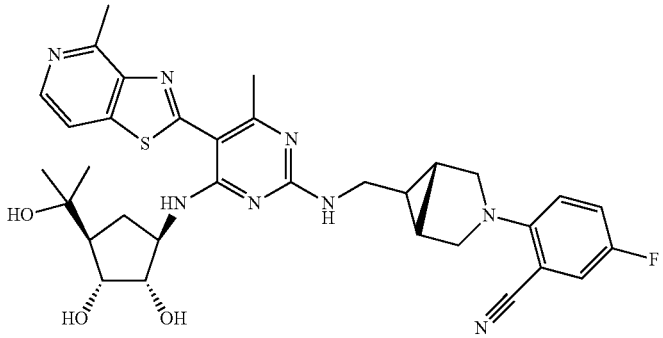
Compd #	Structure	LC-MS or MS $(M + H)^+$
4206		603.3
4207		672.4
4208		617.3
4210		645.4

TABLE IIIA-continued

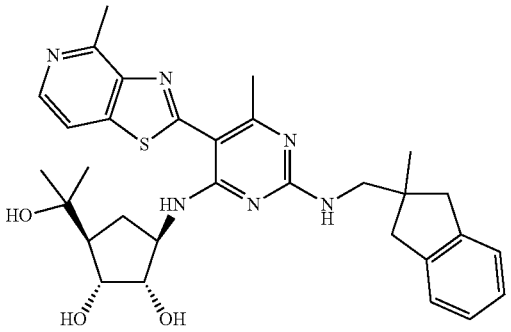
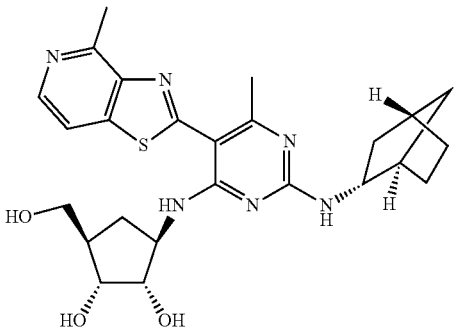
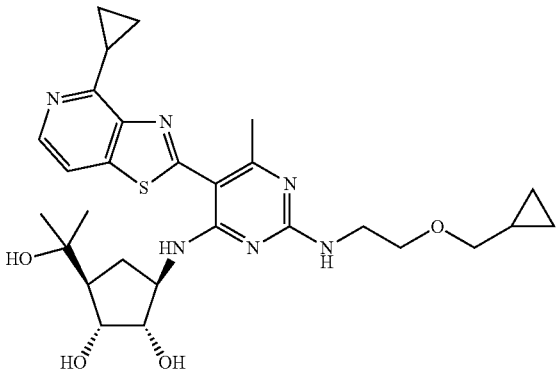
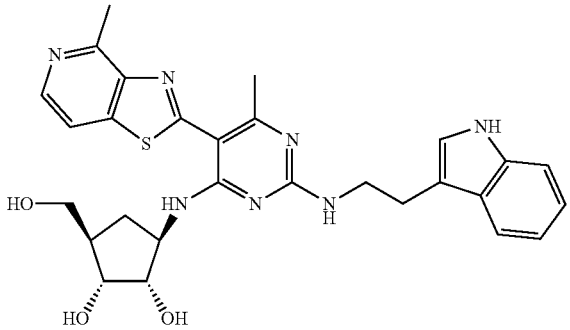
Compd #	Structure	LC-MS or MS $(M + H)^+$
4211		575.3
4212		497.3
4213		555.3
4217		546.3

TABLE IIIA-continued

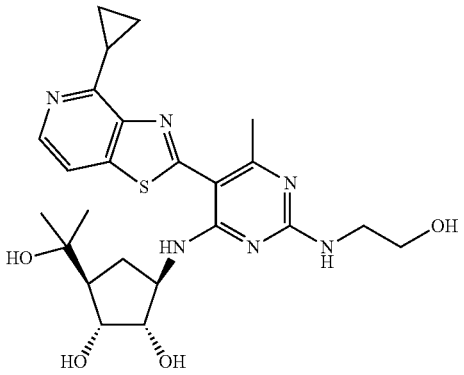
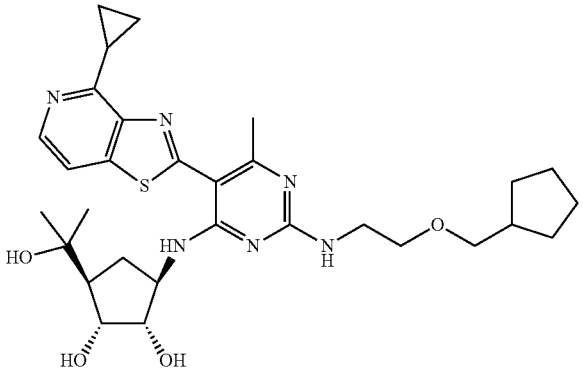
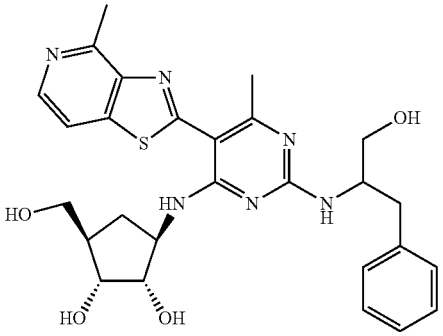
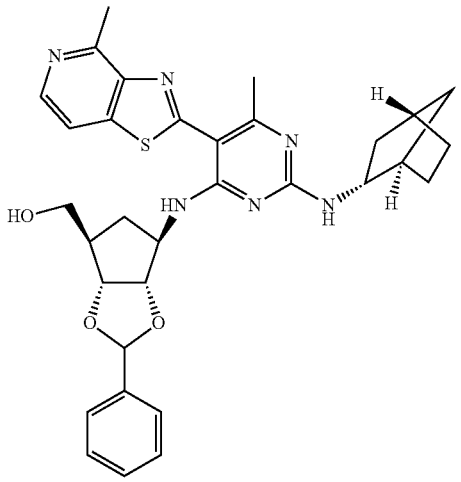
Compd #	Structure	LC-MS or MS $(M + H)^+$
4220		501.3
4221		583.3
4223		537.3
4225		585.3

TABLE IIIA-continued

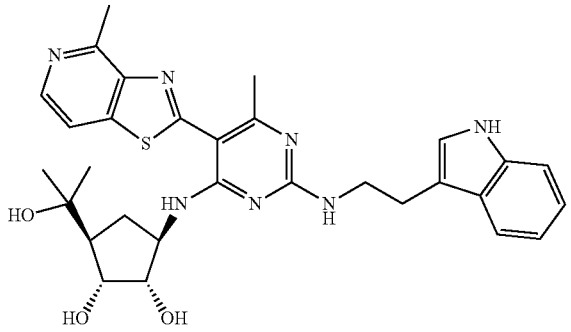
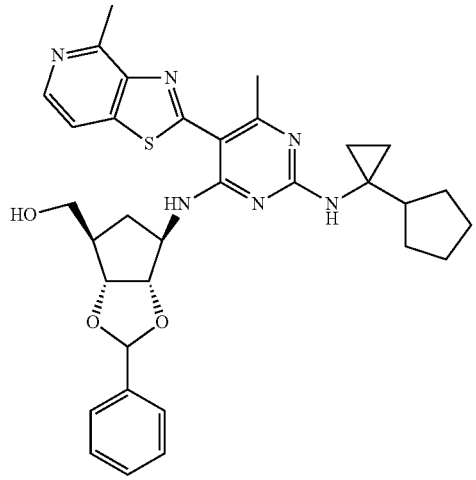
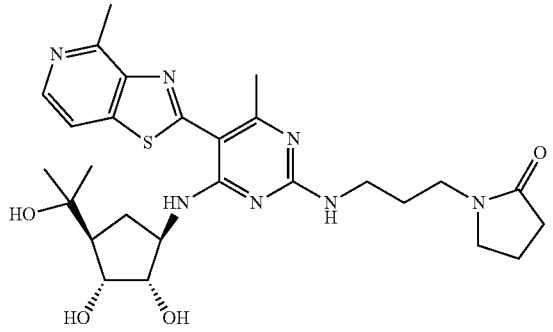
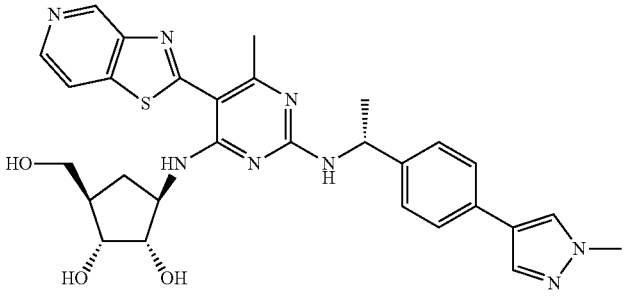
Compd #	Structure	LC-MS or MS $(M + H)^+$
4227		574.3
4228		599.3
4229		556.3
4301		573.3

TABLE IIIA-continued

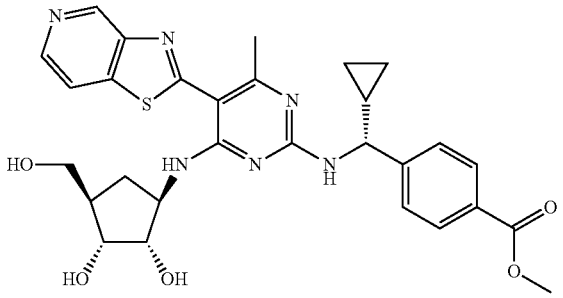
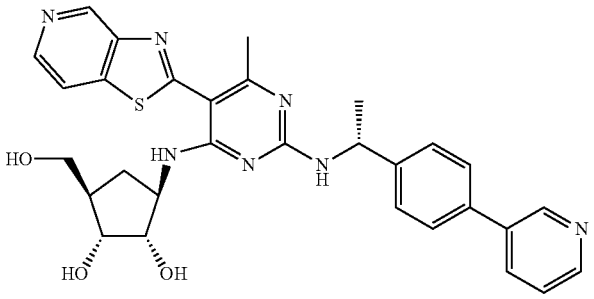
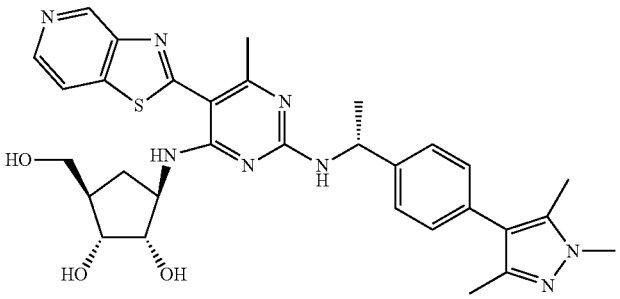
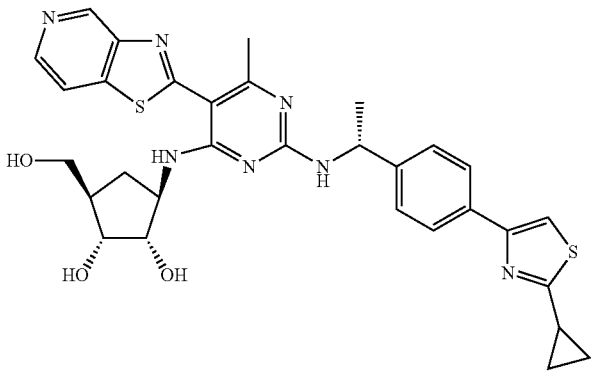
Compd #	Structure	LC-MS or MS $(M + H)^+$
4302		577.3
4303		570.3
4304		601.3
4305		616.3

TABLE IIIA-continued

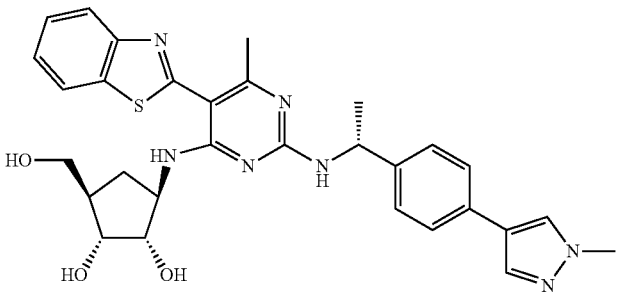
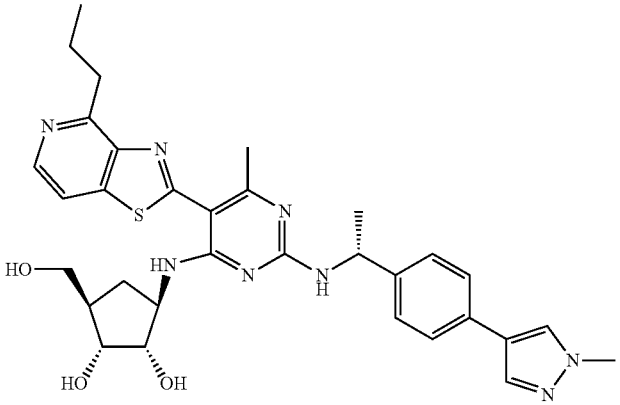
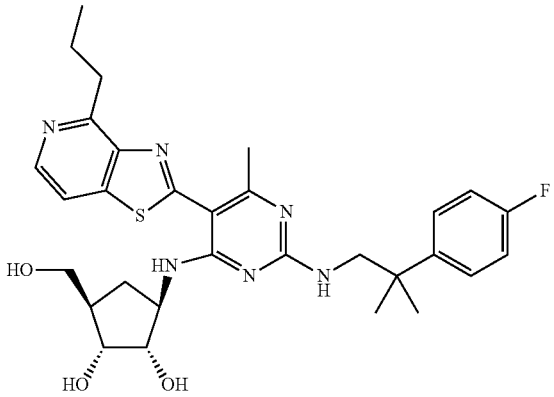
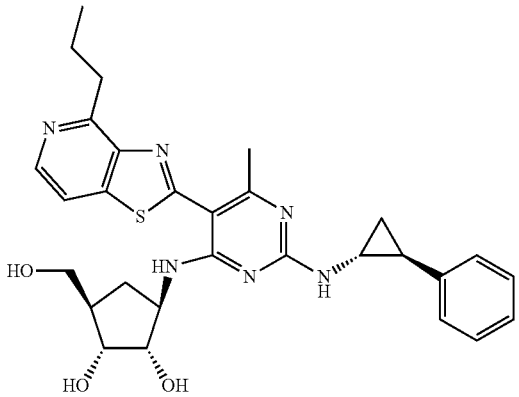
Compd #	Structure	LC-MS or MS $(M + H)^+$
4306		572.3
4307		615.3
4308		581.3
4309		547.3

TABLE IIIA-continued

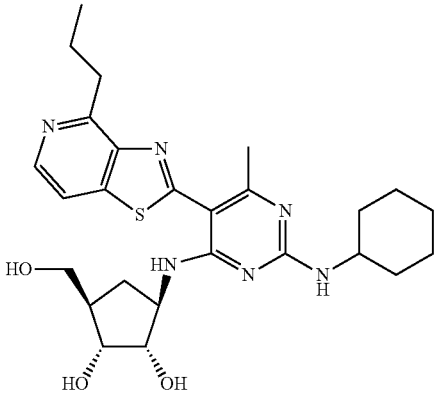
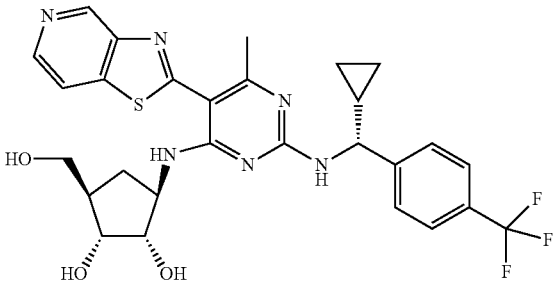
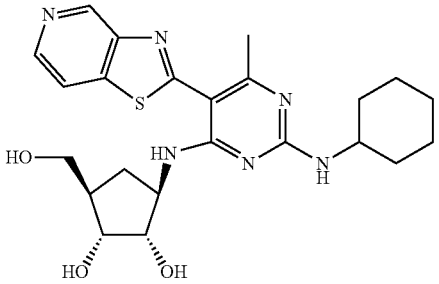
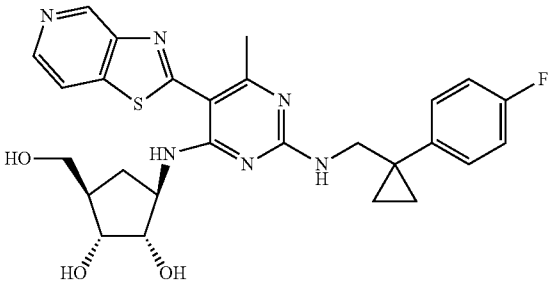
Compd #	Structure	LC-MS or MS $(M + H)^+$
4310		513.3
4311		587.3
4312		471.3
4316		537.2

TABLE IIIA-continued

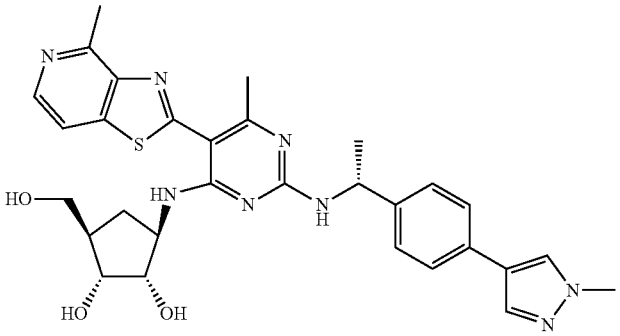
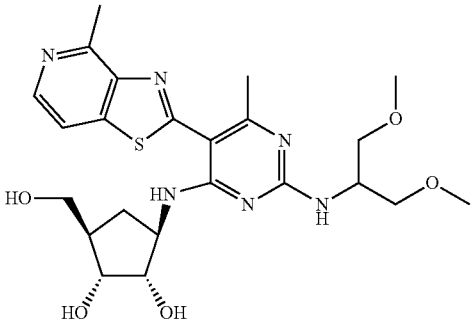
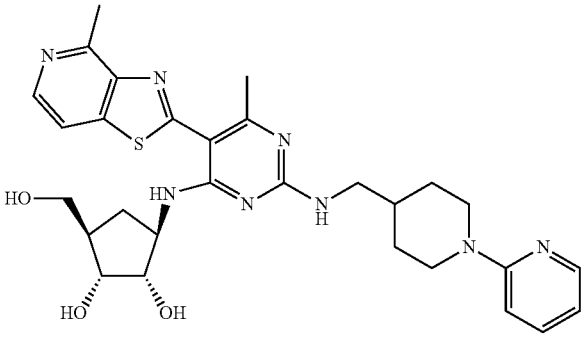
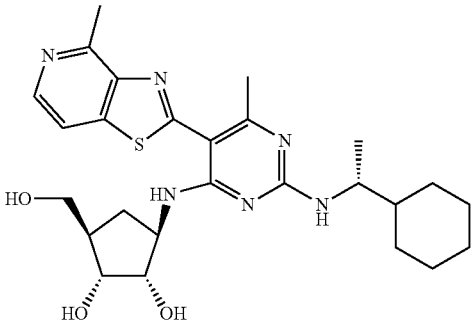
Compd #	Structure	LC-MS or MS $(M + H)^+$
4319		587.3
4320		505.3
4321		577.3
4322		513.3

TABLE IIIA-continued

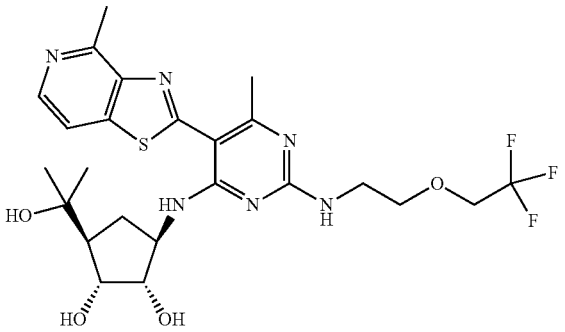
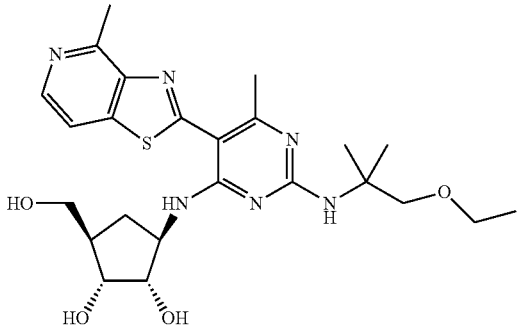
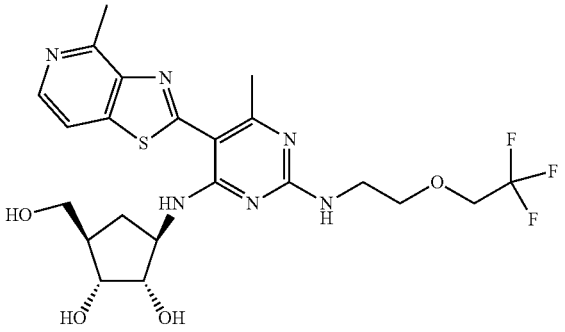
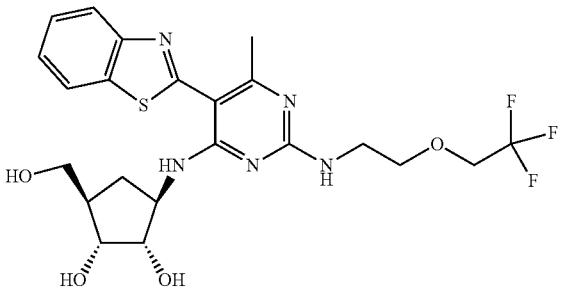
Compd #	Structure	LC-MS or MS $(M + H)^+$
4323		557.2
4324		503.3
4325		529.3
4326		514.3

TABLE IIIA-continued

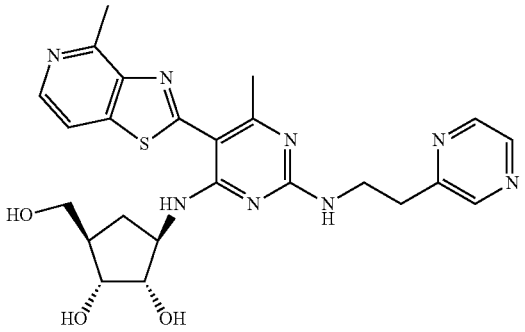
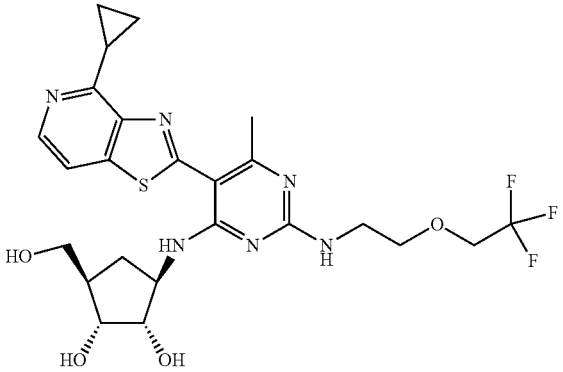
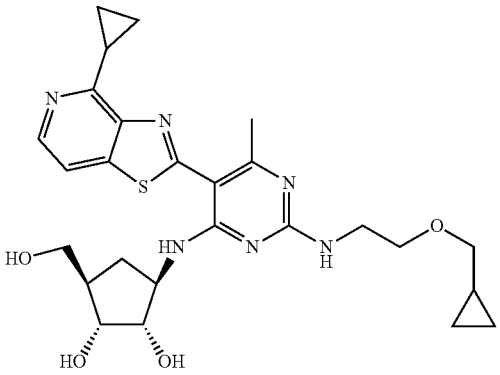
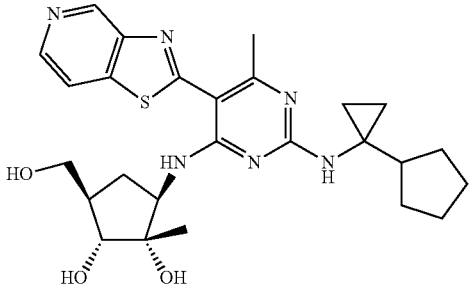
Compd #	Structure	LC-MS or MS $(M + H)^+$
4327		509.2
4328		555.2
4329		527.3
4330		511.2

TABLE IIIA-continued

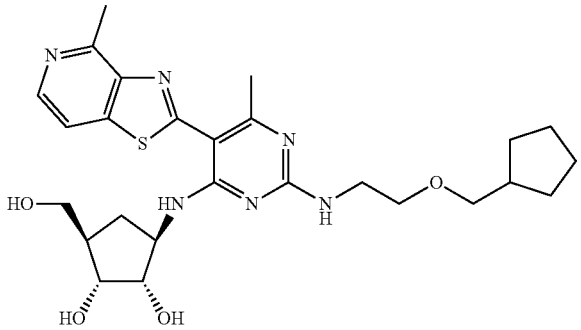
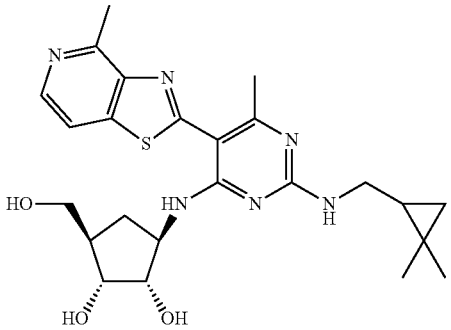
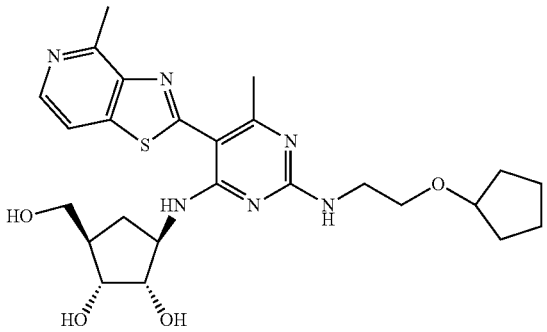
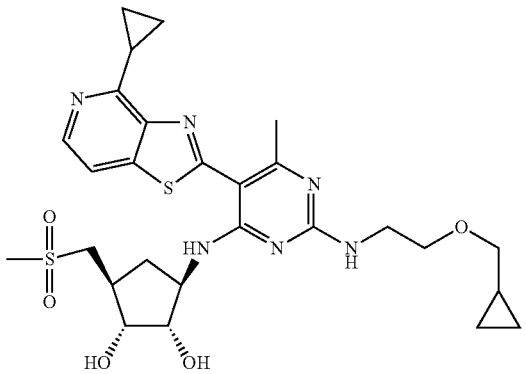
Compd #	Structure	LC-MS or MS $(M + H)^+$
4331		529.2
4332		485.2
4333		515.2
4334		589.2

TABLE IIIA-continued

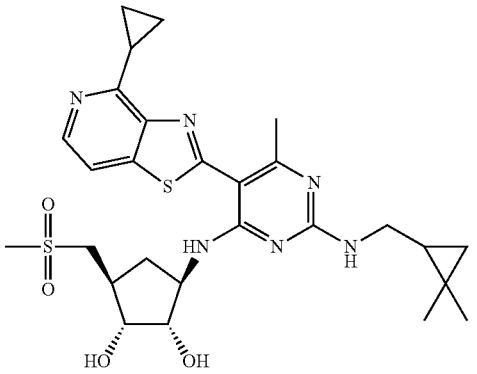
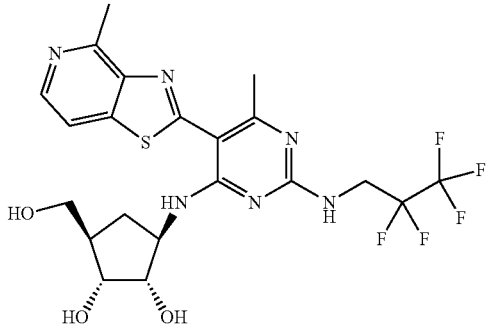
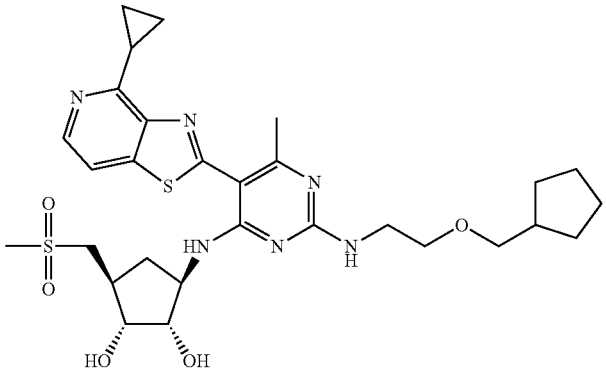
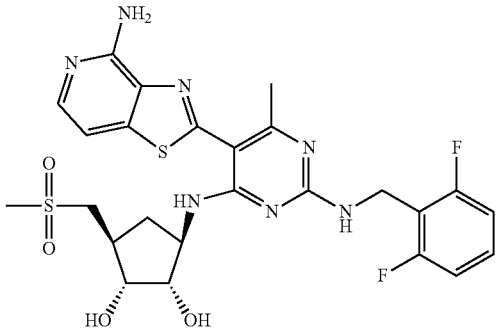
Compd #	Structure	LC-MS or MS $(M + H)^+$
4335		573.3
4336		535.2
4337		617.3
4338		592.2

TABLE IIIA-continued

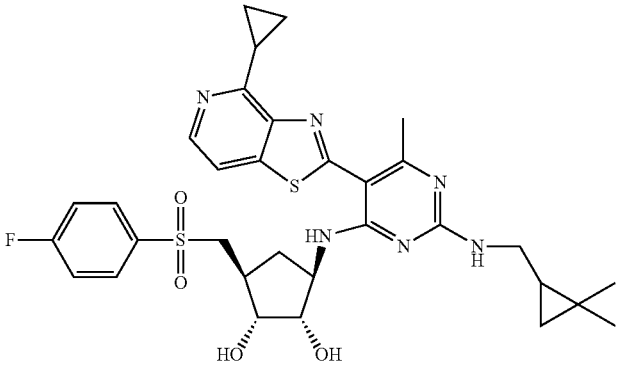
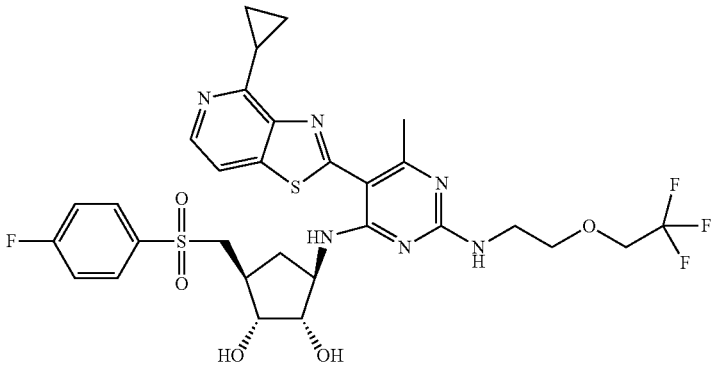
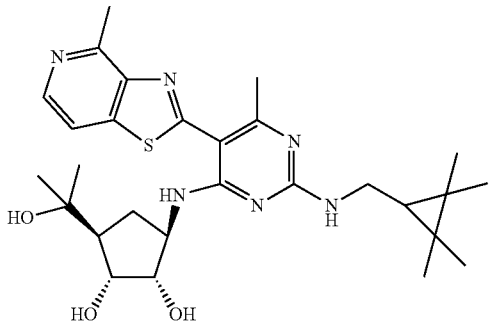
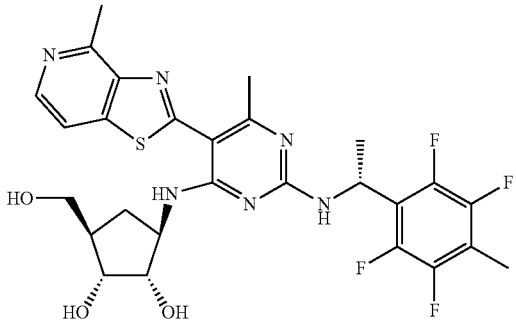
Compd #	Structure	LC-MS or MS $(M + H)^+$
4339		653.2
4340		697.2
4341		541.3
4342		593.2

TABLE IIIA-continued

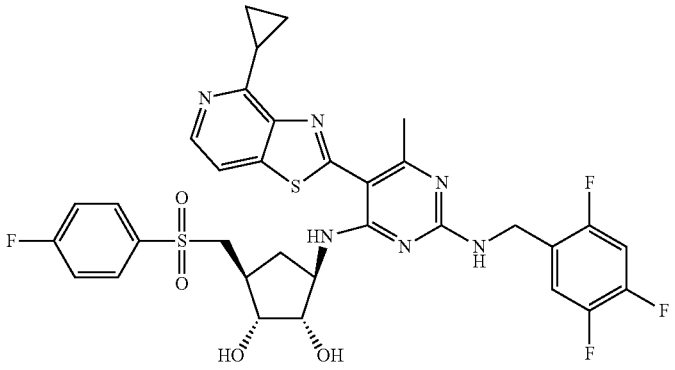
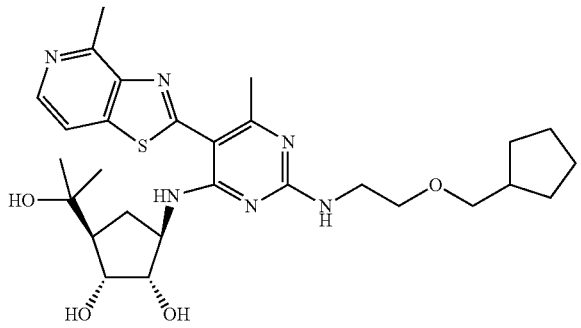
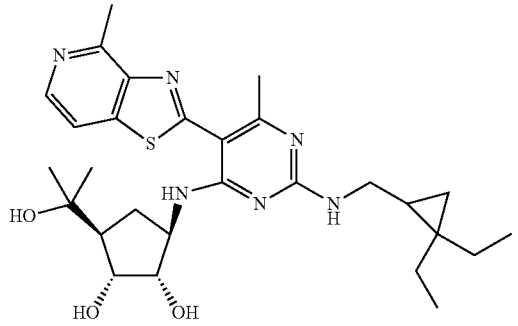
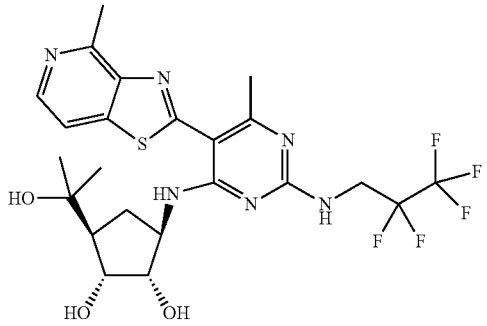
Compd #	Structure	LC-MS or MS $(M + H)^+$
4343		716.2
4344		557
4345		541.3
4346		563.2

TABLE IIIA-continued

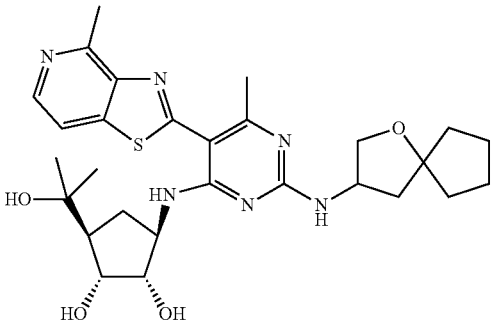
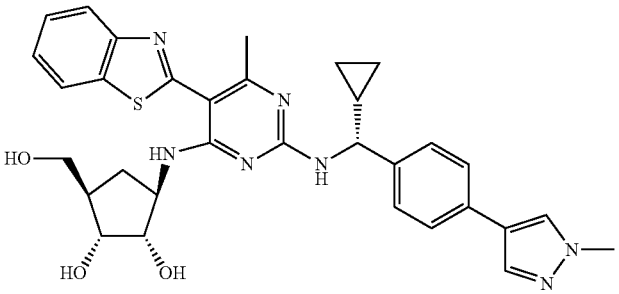
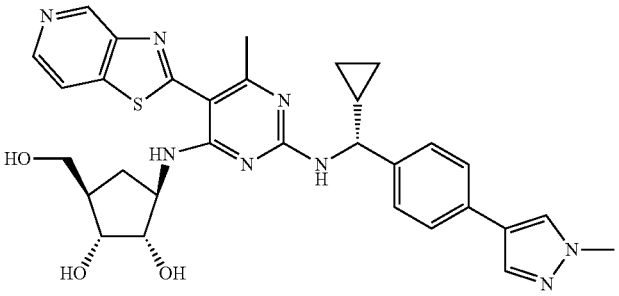
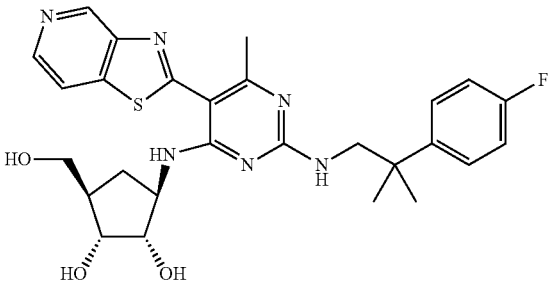
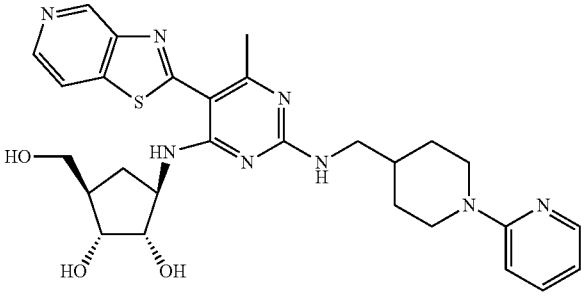
Compd #	Structure	LC-MS or MS $(M + H)^+$
4347		555.3
4404		598.3
4405		599.3
4406		539.3
4407		563.3

TABLE IIIA-continued

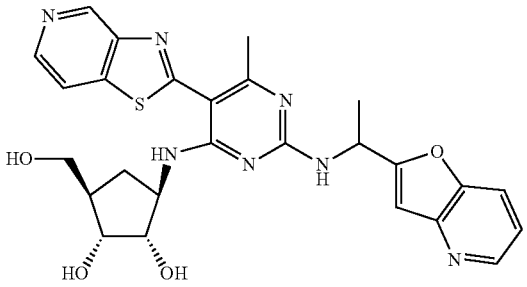
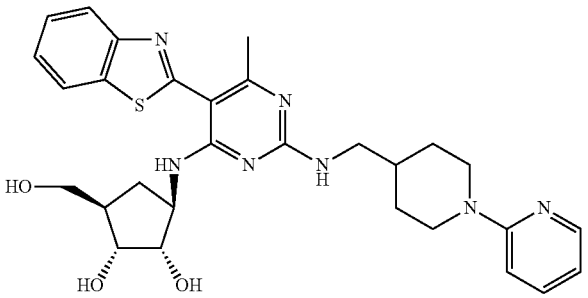
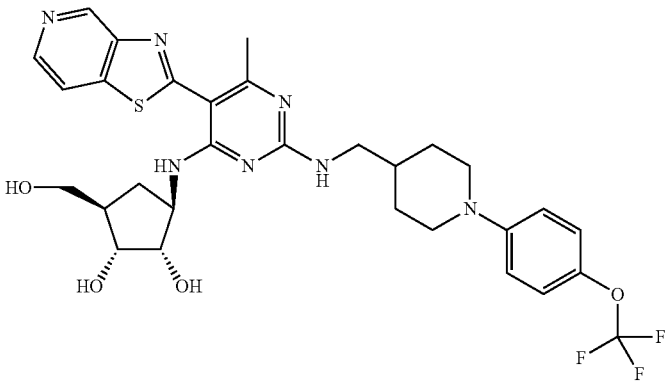
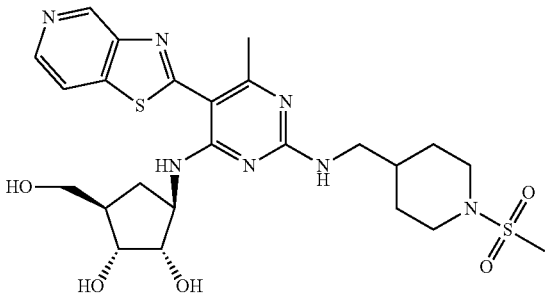
Compd #	Structure	LC-MS or MS $(M + H)^+$
4409		534.3
4410		562.3
4411		646.4
4412		564.3

TABLE IIIA-continued

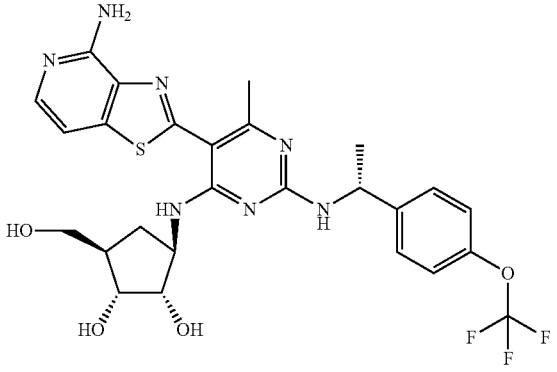
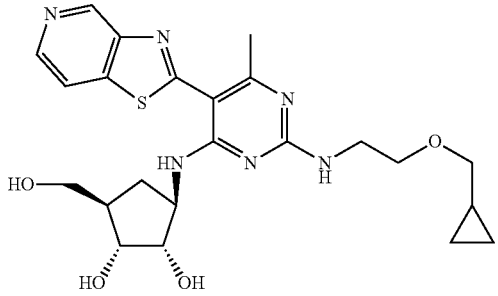
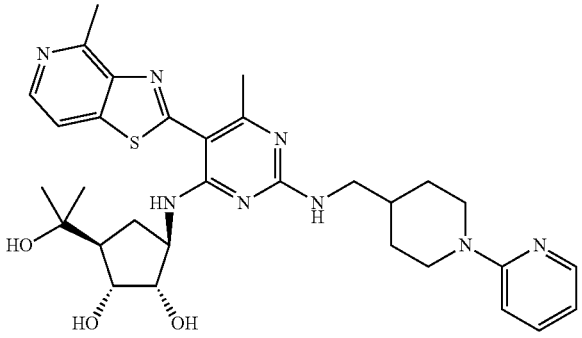
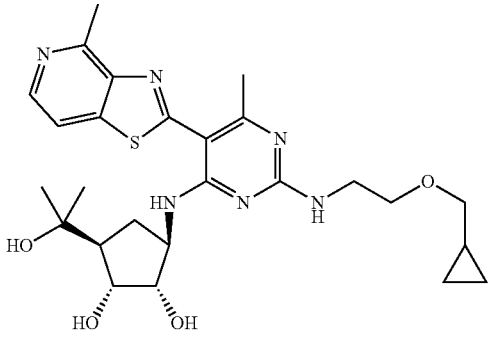
Compd #	Structure	LC-MS or MS $(M + H)^+$
4413		592.3
4414		487.3
4415		605.3
4416		529.3

TABLE IIIA-continued

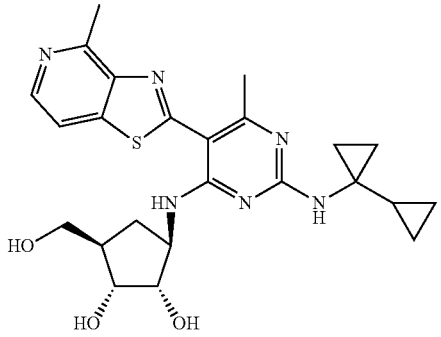
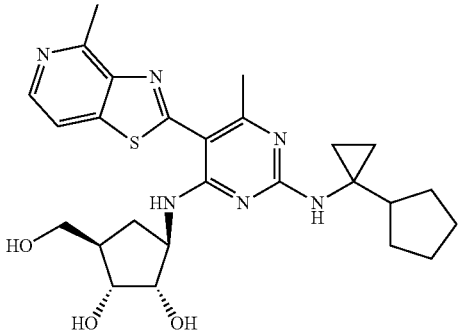
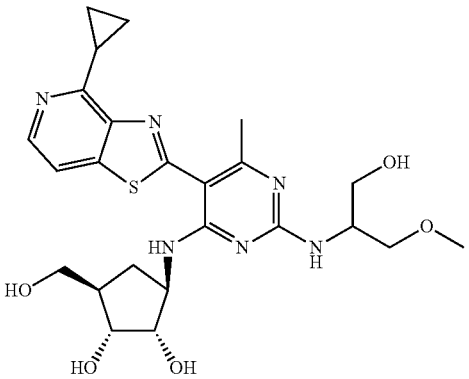
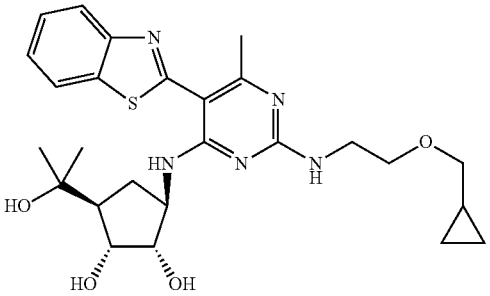
Compd #	Structure	LC-MS or MS $(M + H)^+$
4417		483.3
4418		511.3
4420		517.3
4421		514.3

TABLE IIIA-continued

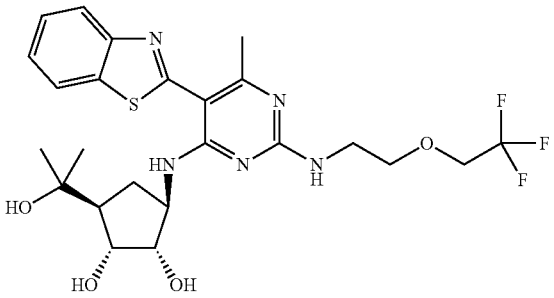
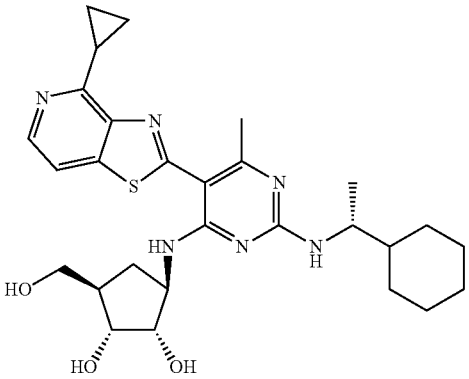
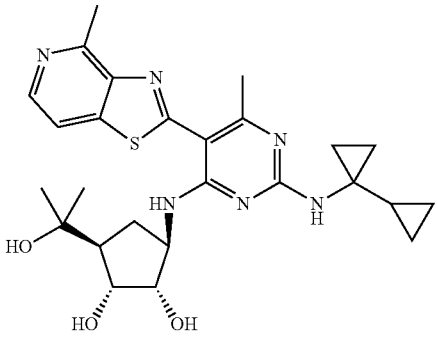
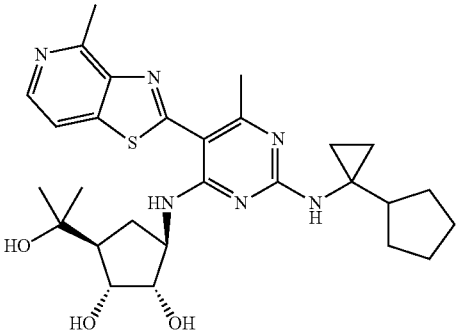
Compd #	Structure	LC-MS or MS $(M + H)^+$
4422		542.3
4424		539.3
4425		511.3
4426		539.3

TABLE IIIA-continued

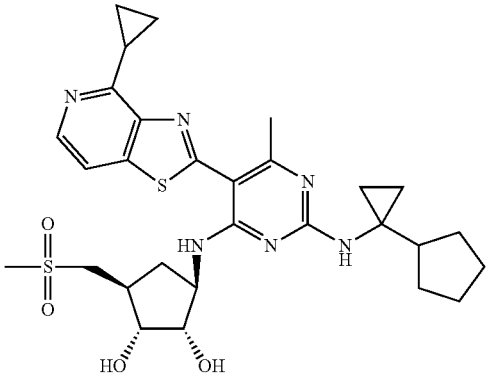
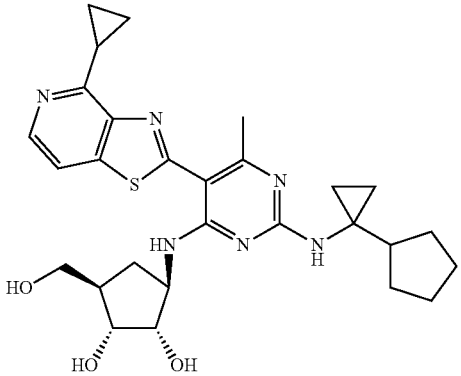
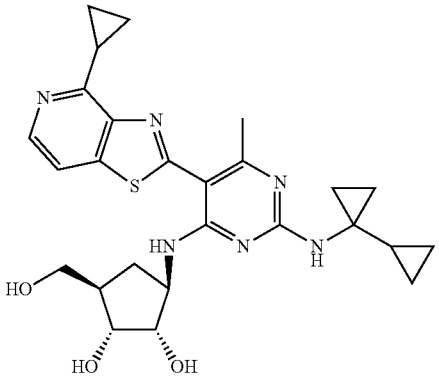
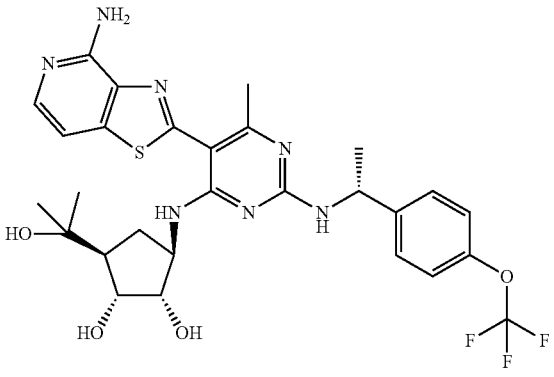
Compd #	Structure	LC-MS or MS $(M + H)^+$
4427		599.3
4428		537.3
4429		509.3
4431		620.3

TABLE IIIA-continued

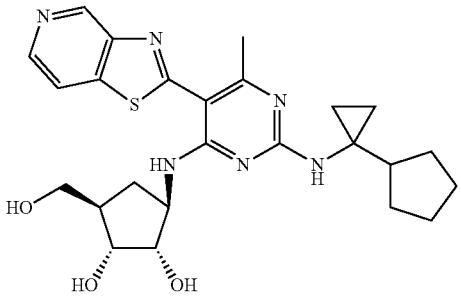
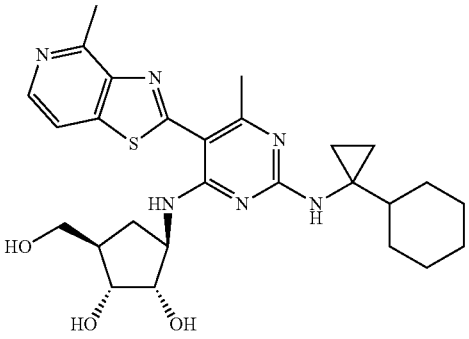
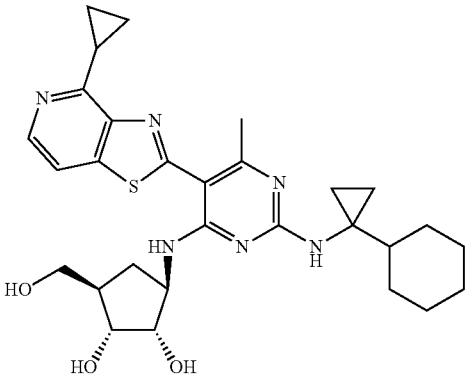
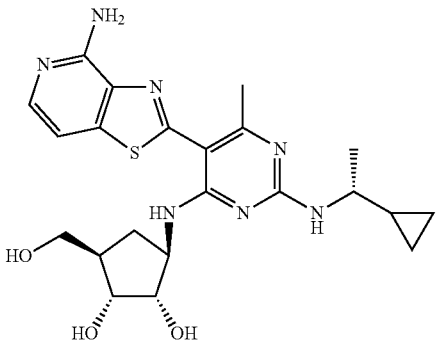
Compd #	Structure	LC-MS or MS $(M + H)^+$
4432		497.3
4433		525.3
4434		551.3
4435		472.3

TABLE IIIA-continued

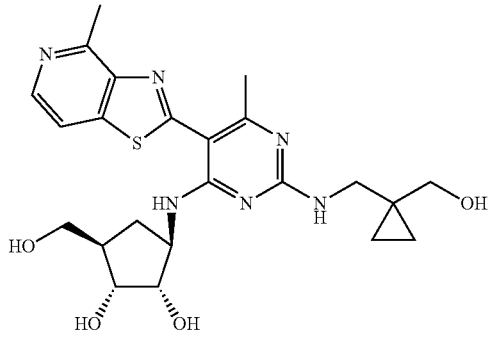
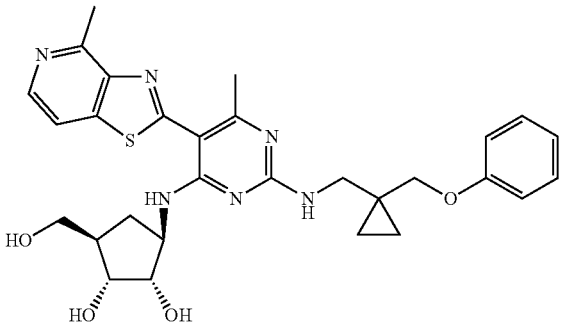
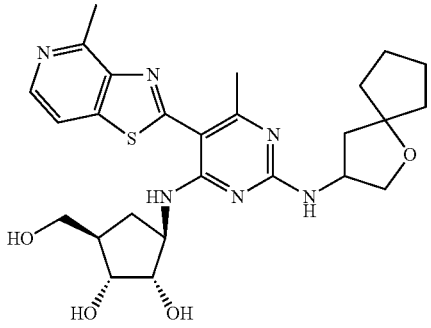
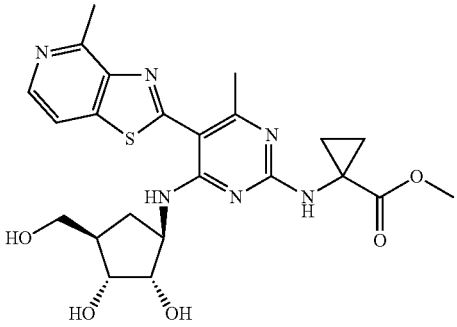
Compd #	Structure	LC-MS or MS $(M + H)^+$
4436		487.3
4437		563.3
4438		527.3
4439		501.3

TABLE IIIA-continued

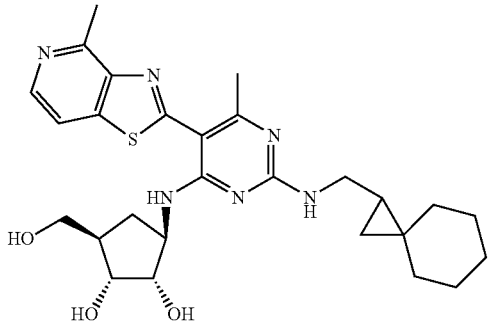
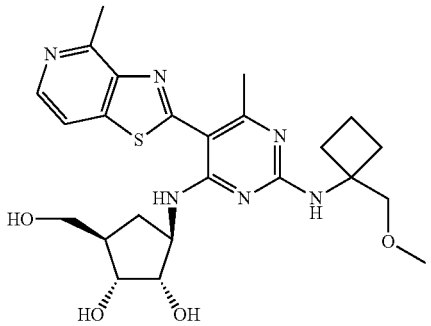
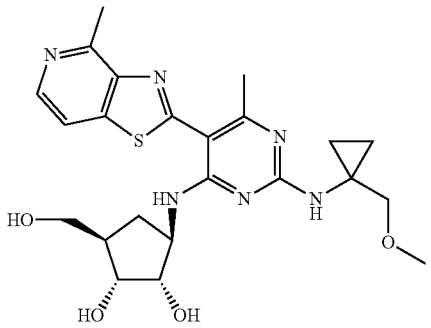
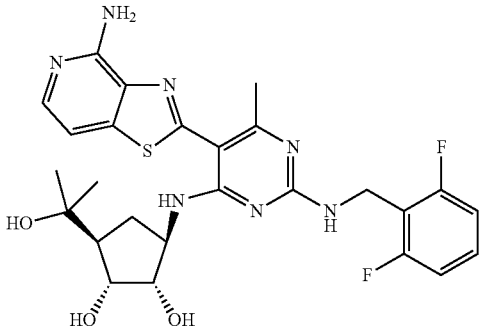
Compd #	Structure	LC-MS or MS $(M + H)^+$
4440		525.3
4441		501.3
4442		487.3
4443		558.3

TABLE IIIA-continued

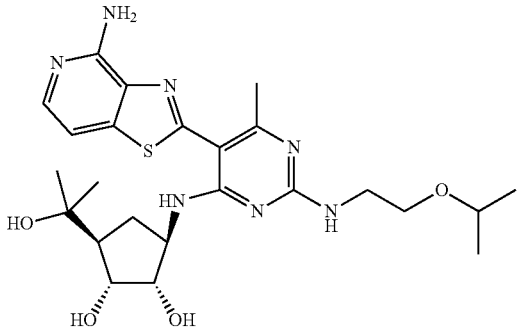
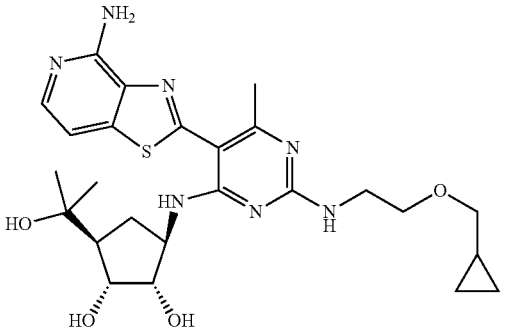
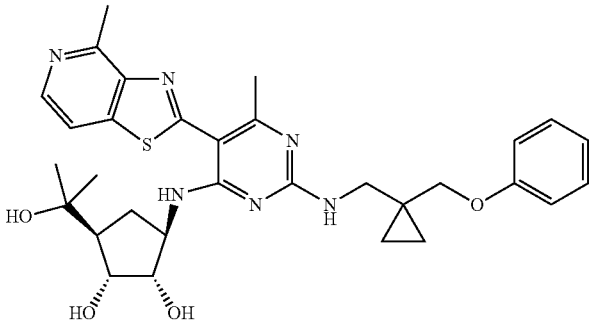
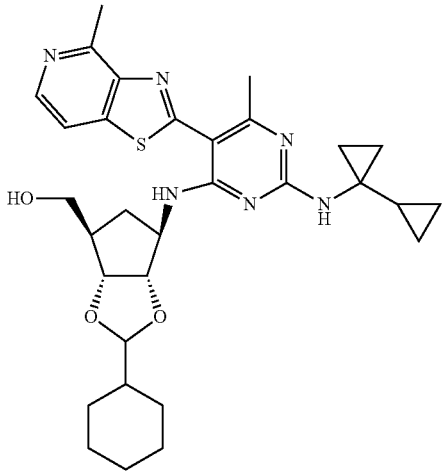
Compd #	Structure	LC-MS or MS $(M + H)^+$
4444		518.3
4445		530.3
4446		591.3
4447		577.3

TABLE IIIA-continued

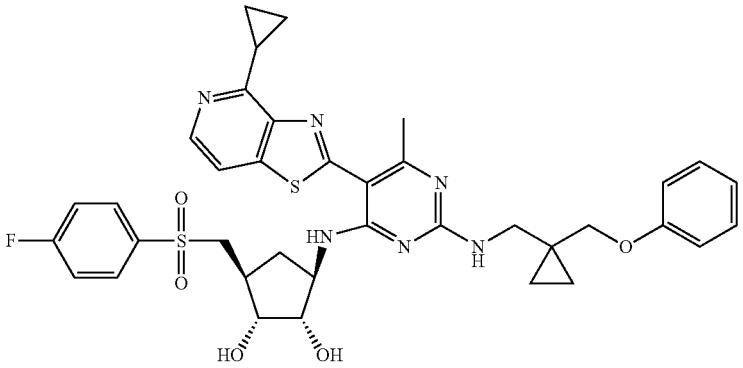
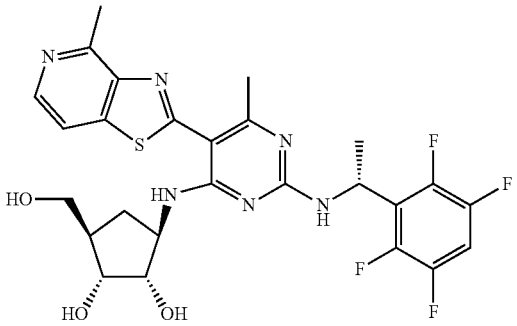
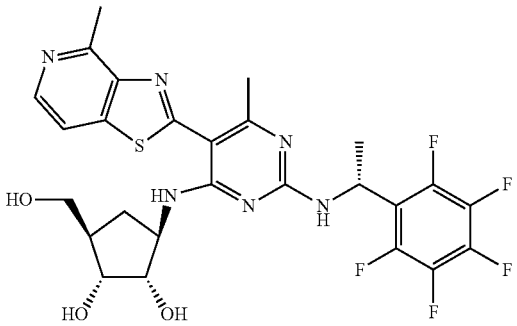
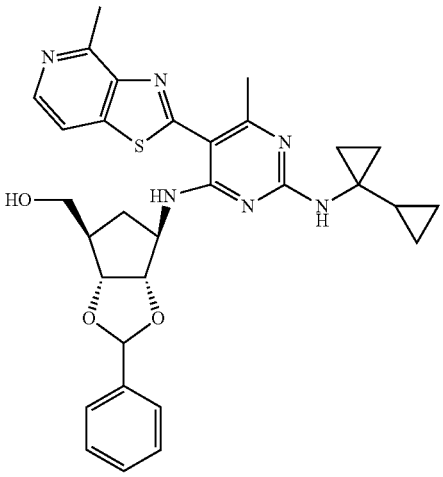
Compd #	Structure	LC-MS or MS $(M + H)^+$
4448		731.4
4449		579.3
4450		597.3
4451		571.3

TABLE IIIA-continued

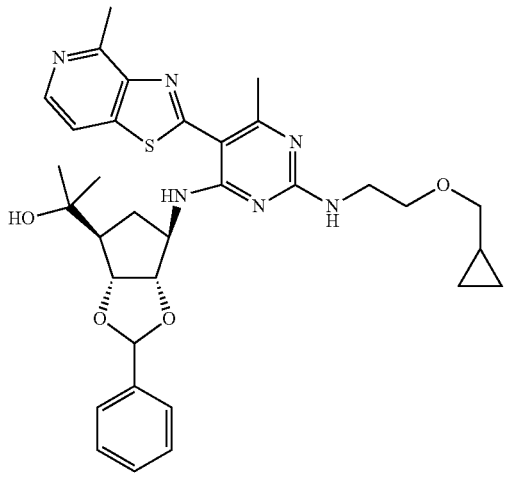
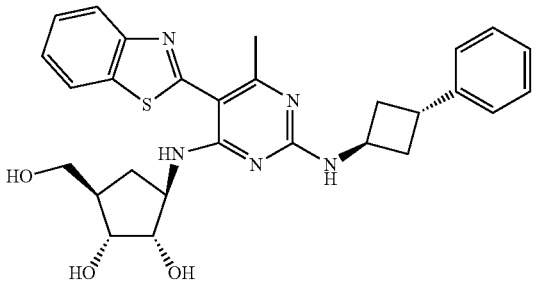
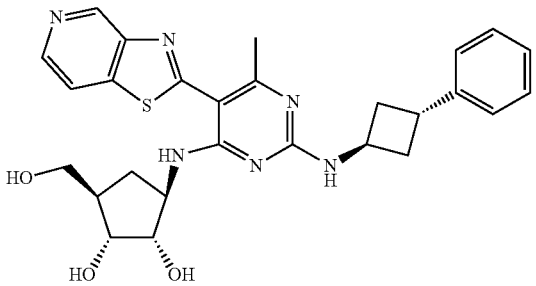
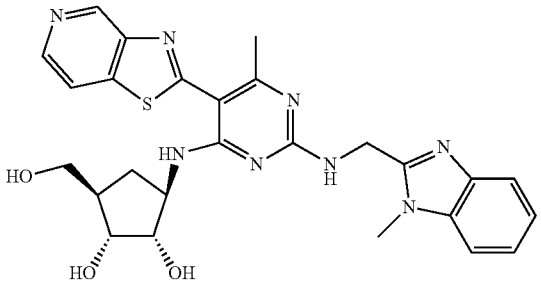
Compd #	Structure	LC-MS or MS $(M + H)^+$
4453		617.3
4503		518.2
4505		519.2
4506		533.2

TABLE IIIA-continued

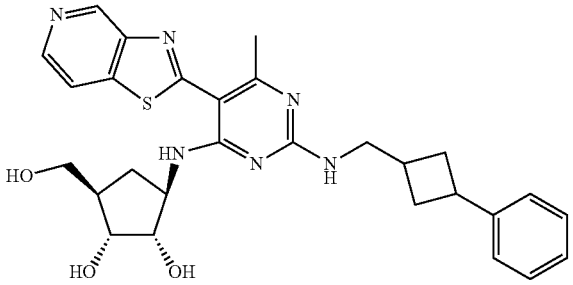
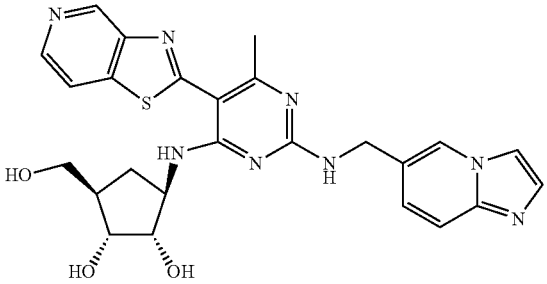
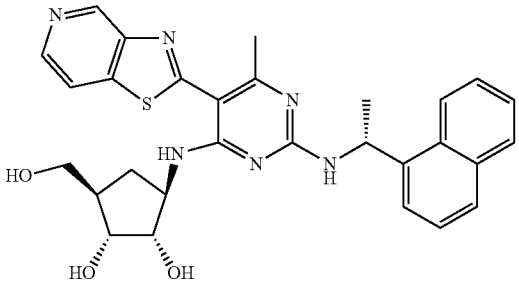
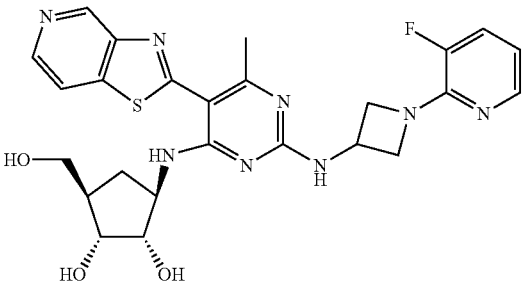
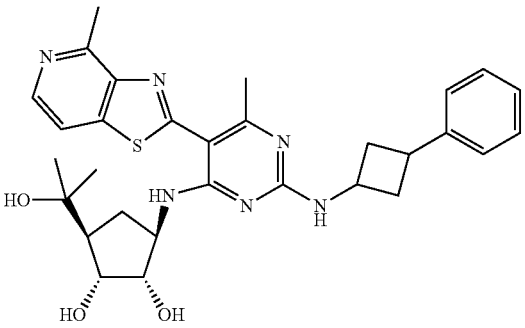
Compd #	Structure	LC-MS or MS $(M + H)^+$
4507		533.7
4508		519.2
4509		543.2
4510		539.2
4511		561.7

TABLE IIIA-continued

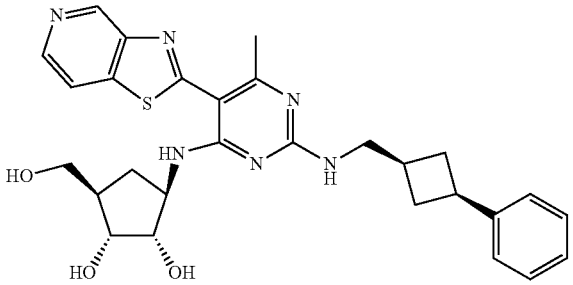
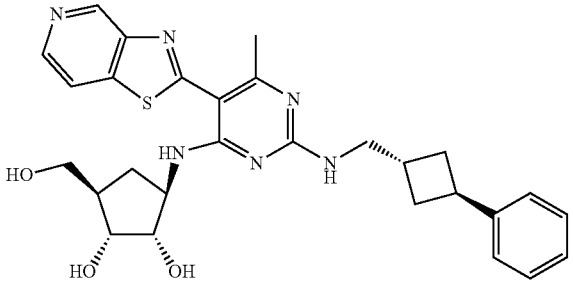
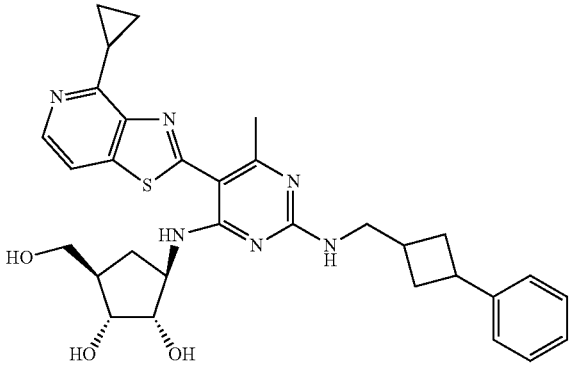
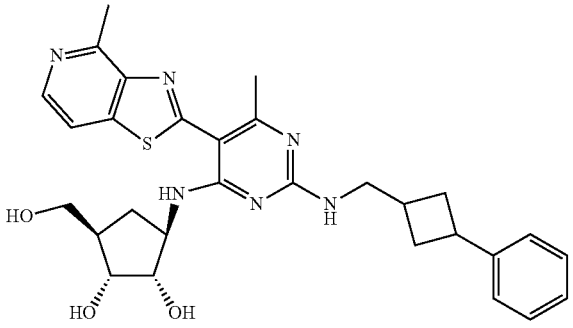
Compd #	Structure	LC-MS or MS $(M + H)^+$
4512		533.3
4513		533.3
4515		573.2
4516		547.2

TABLE IIIA-continued

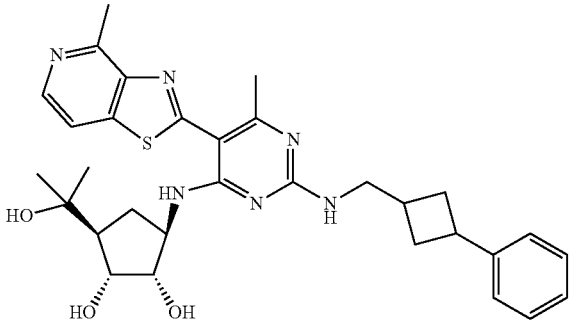
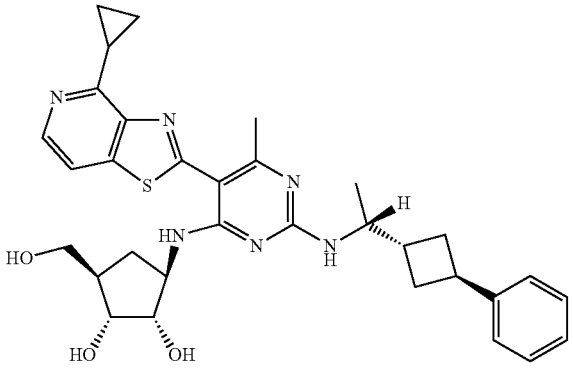
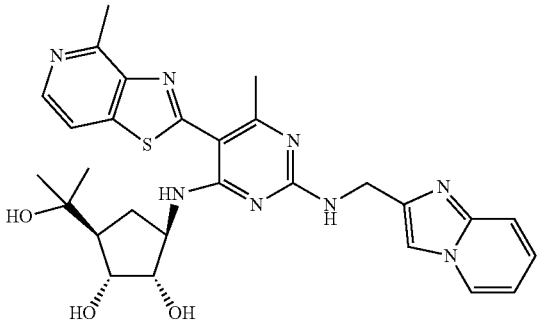
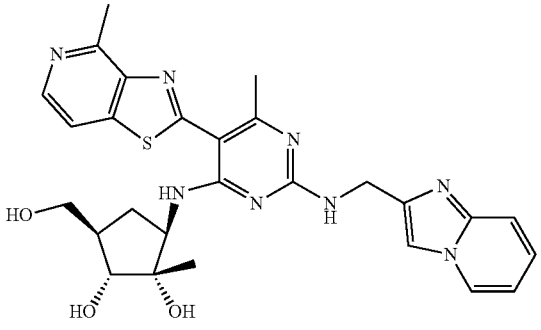
Compd #	Structure	LC-MS or MS $(M + H)^+$
4517		545.2
4518		547.2
4520		561.3
4521		547.3

TABLE IIIA-continued

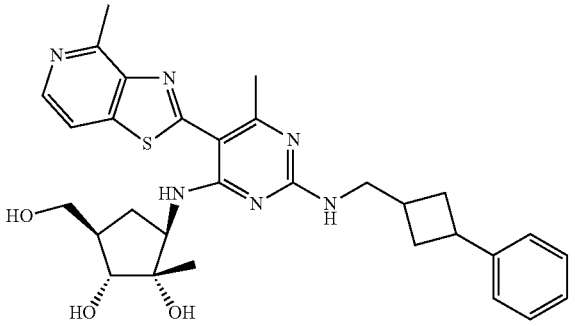
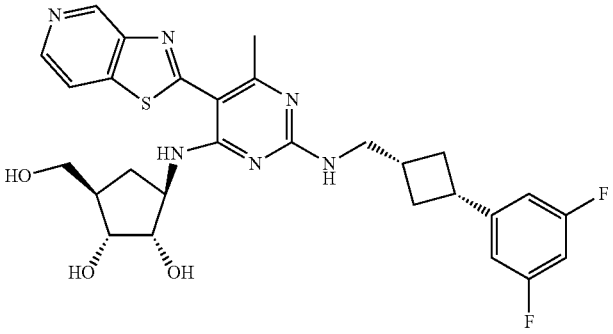
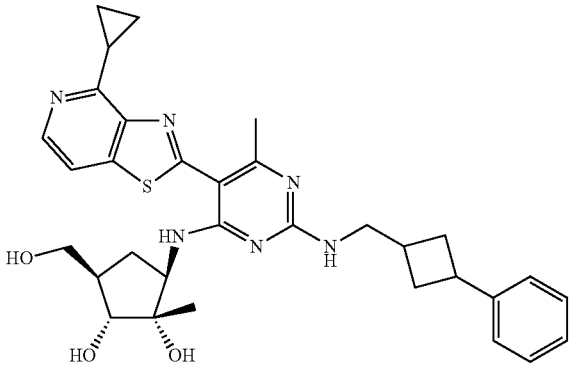
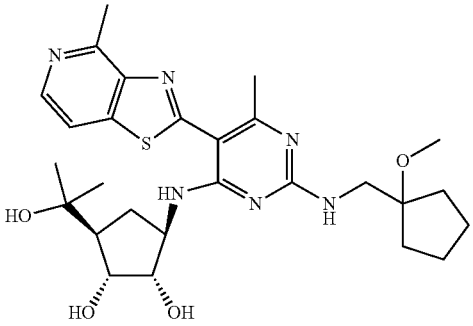
Compd #	Structure	LC-MS or MS $(M + H)^+$
4522		561.2
4523		569.2
4524		587.3
4527		543.3

TABLE IIIA-continued

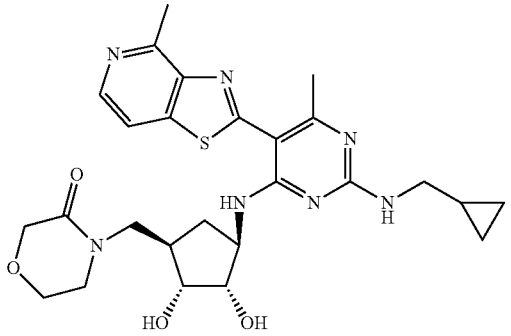
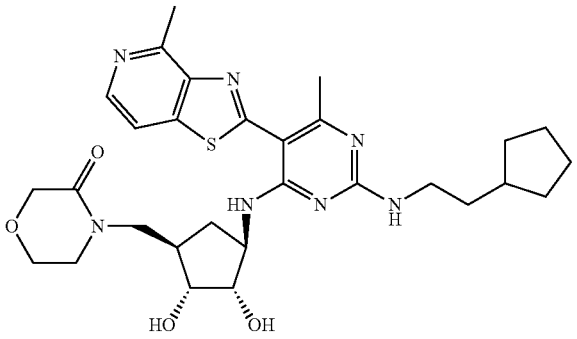
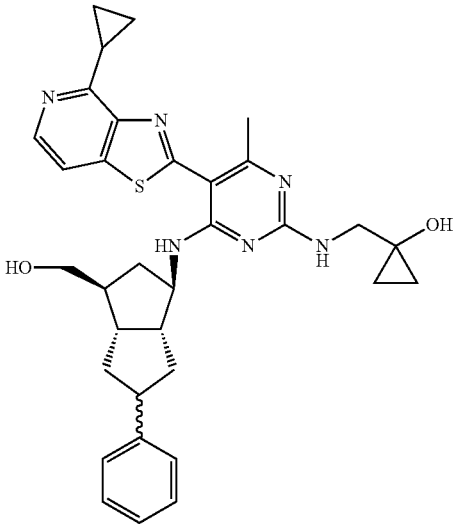
Compd #	Structure	LC-MS or MS $(M + H)^+$
4530		540.3
4531		582.2
4532		587.3

TABLE IIIA-continued

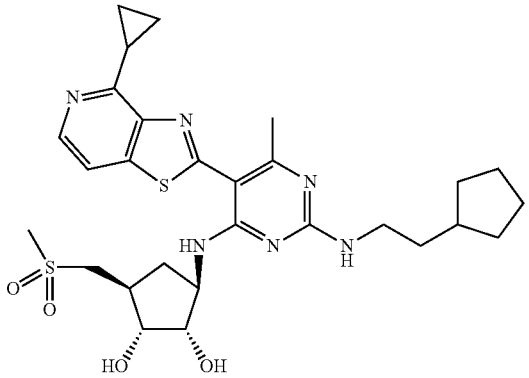
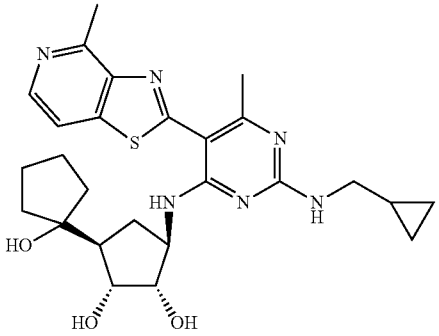
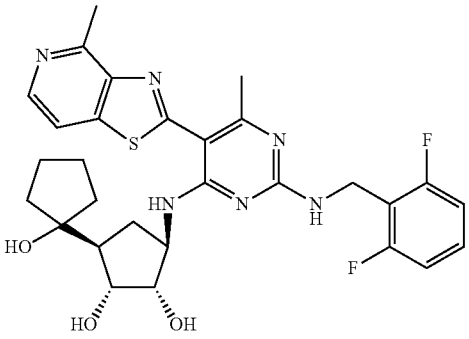
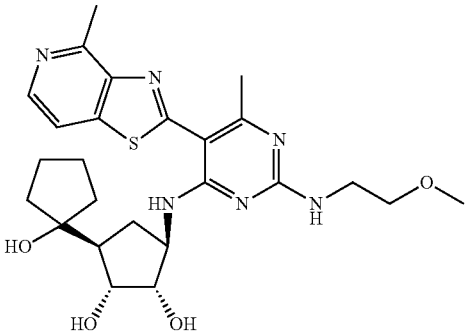
Compd #	Structure	LC-MS or MS $(M + H)^+$
4533		587.2
4534		511.3
4535		583.2
4536		515.3

TABLE IIIA-continued

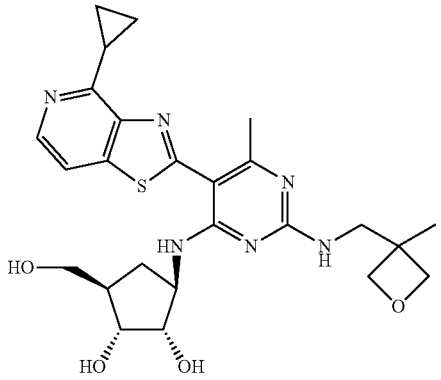
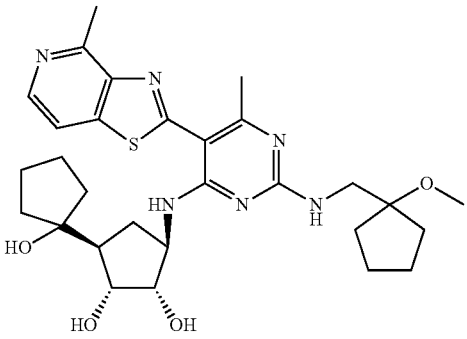
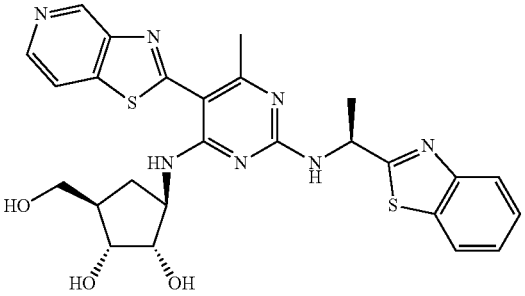
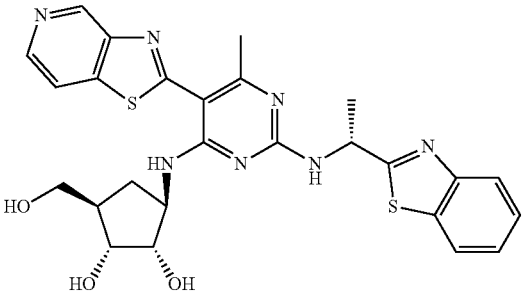
Compd #	Structure	LC-MS or MS $(M + H)^+$
4537		513.2
4538		569.3
4601		550.3
4602		550.3

TABLE IIIA-continued

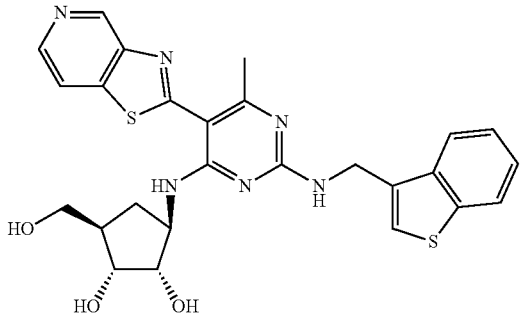
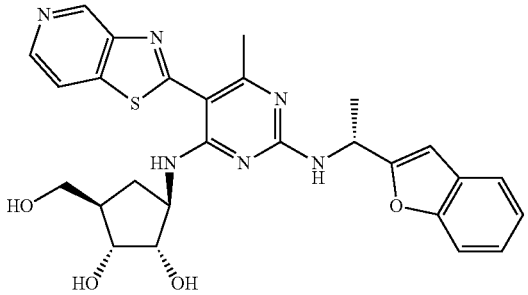
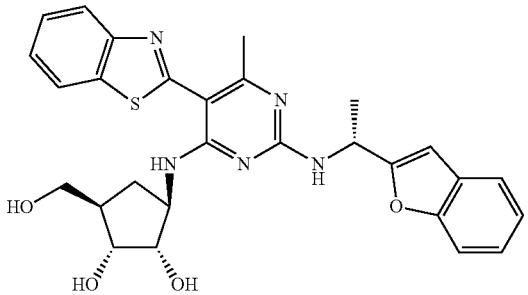
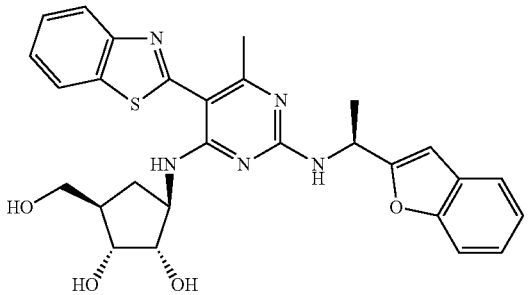
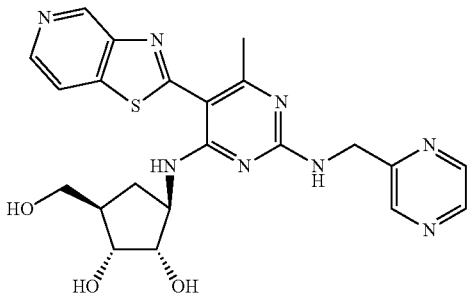
Compd #	Structure	LC-MS or MS $(M + H)^+$
4603		535.3
4607		533.3
4608		532.3
4611		532.3
4614		481.3

TABLE IIIA-continued

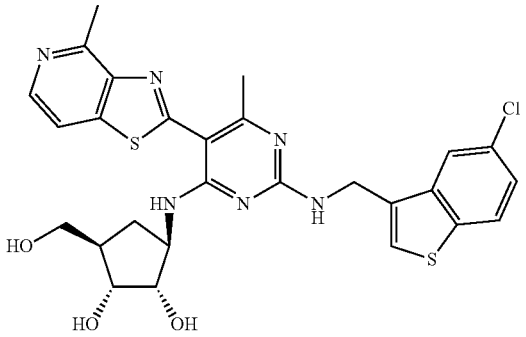
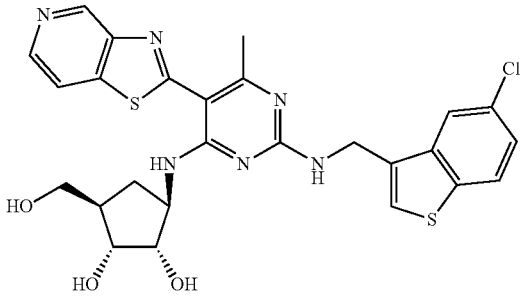
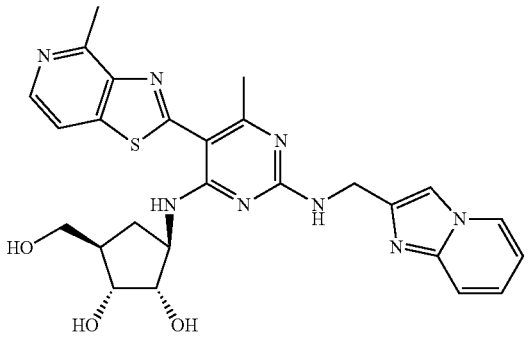
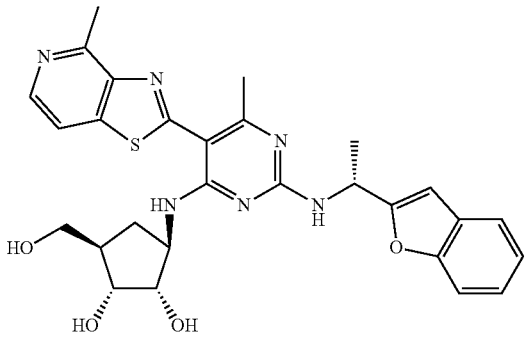
Compd #	Structure	LC-MS or MS $(M + H)^+$
4615		583.3
4616		569.3
4618		533.7
4619		547.3

TABLE IIIA-continued

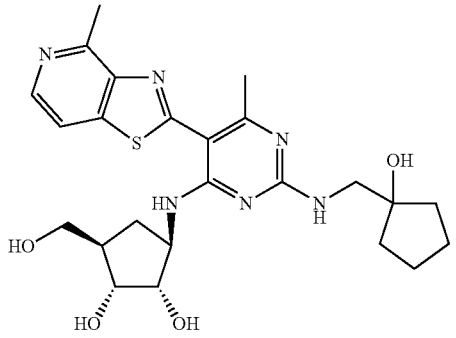
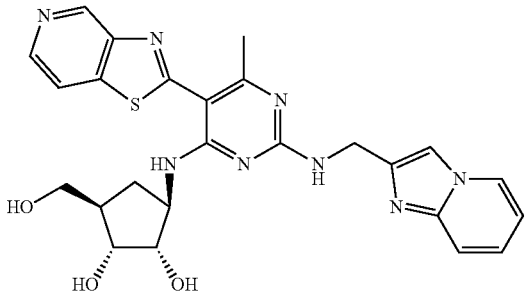
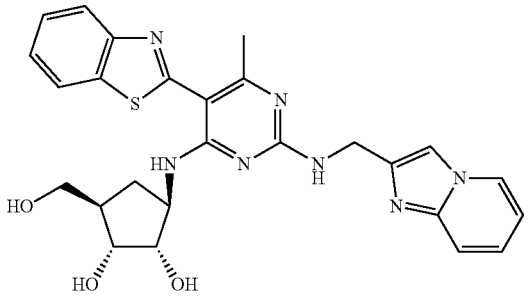
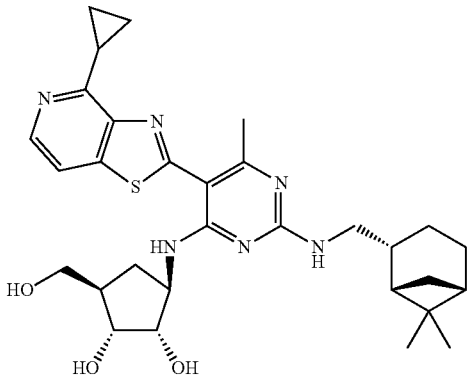
Compd #	Structure	LC-MS or MS $(M + H)^+$
4621		501.7
4623		519.3
4624		518.3
4625		565.7

TABLE IIIA-continued

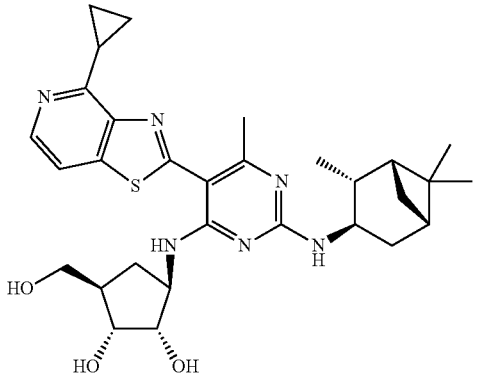
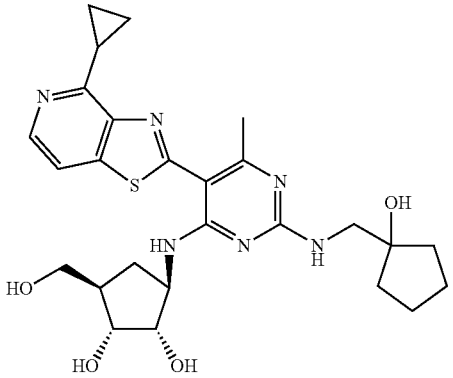
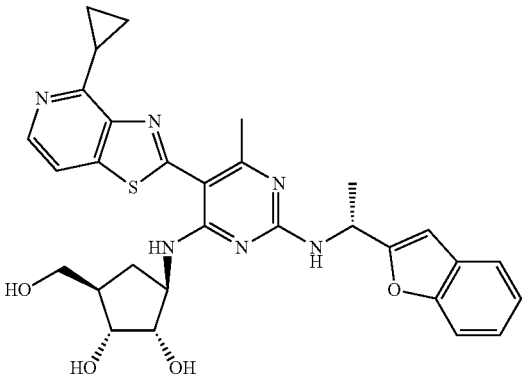
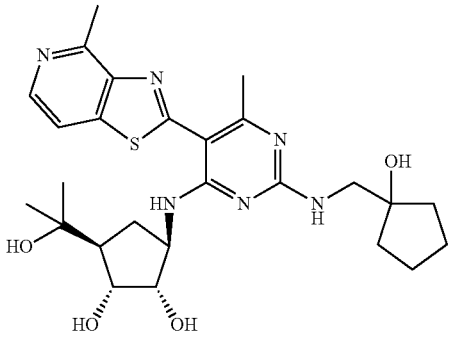
Compd #	Structure	LC-MS or MS $(M + H)^+$
4626		565.7
4627		527.7
4628		573.7
4629		529.7

TABLE IIIA-continued

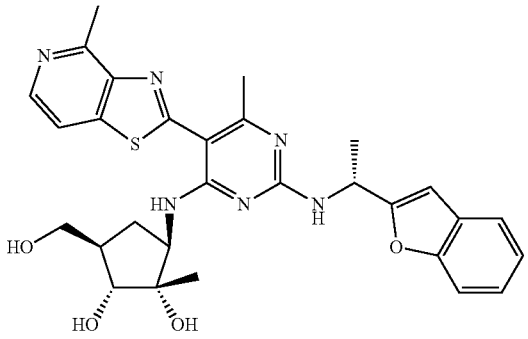
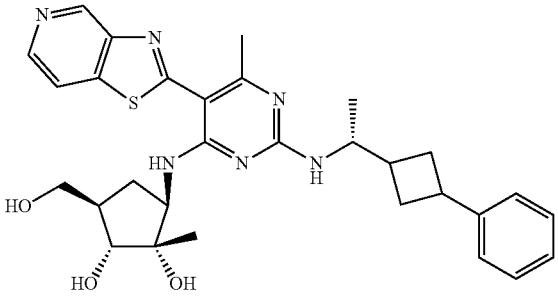
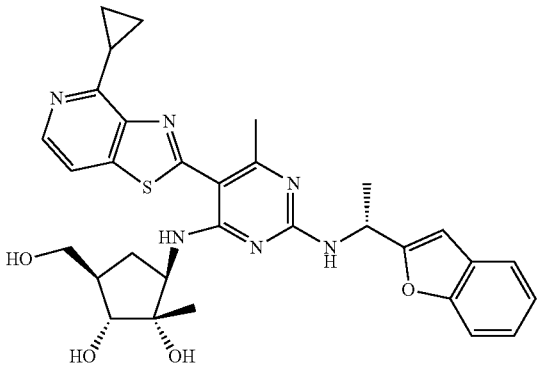
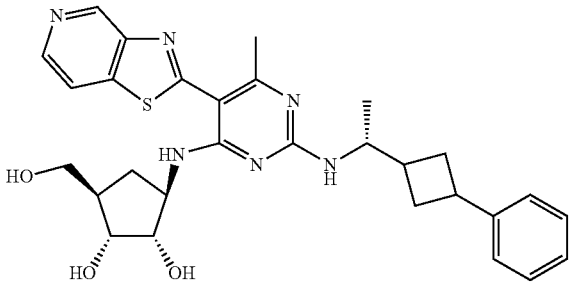
Compd #	Structure	LC-MS or MS $(M + H)^+$
4631		561.7
4632		561.7
4633		587.7
4634		547.7

TABLE IIIA-continued

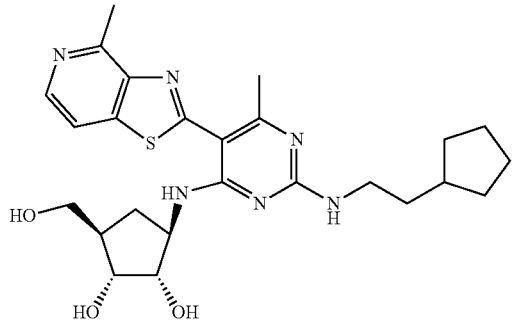
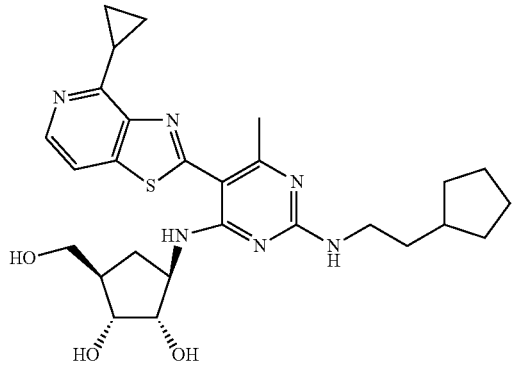
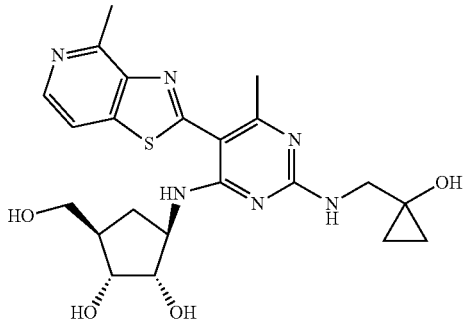
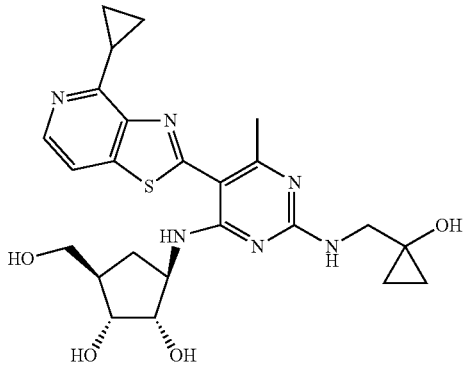
Compd #	Structure	LC-MS or MS $(M + H)^+$
4635		499.7
4636		525.7
4637		473.7
4638		499.7

TABLE IIIA-continued

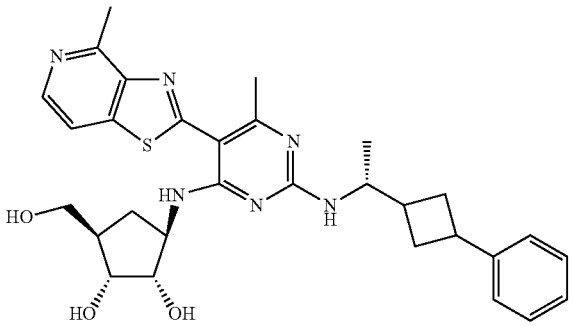
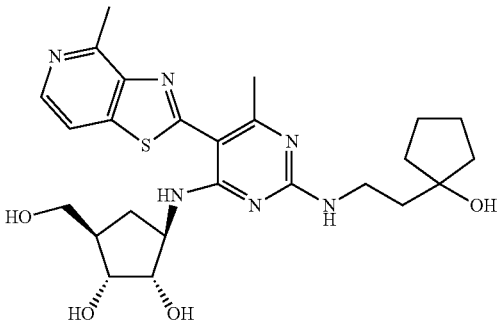
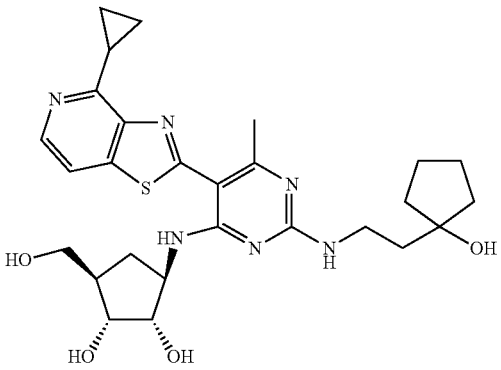
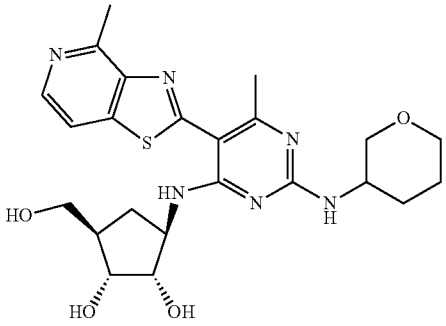
Compd #	Structure	LC-MS or MS $(M + H)^+$
4639		561.7
4640		515.2
4641		541.3
4642		487.7

TABLE IIIA-continued

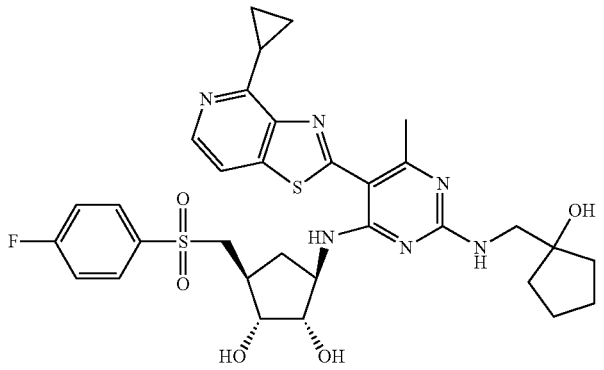
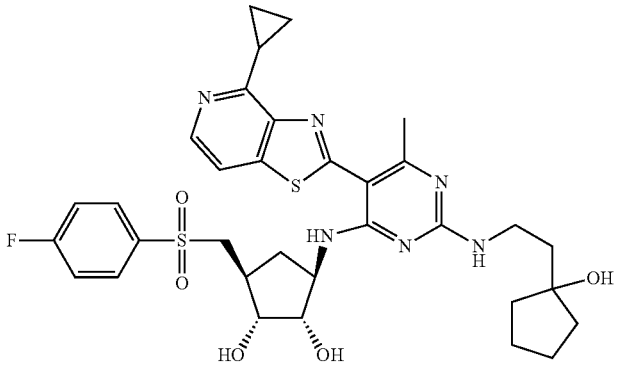
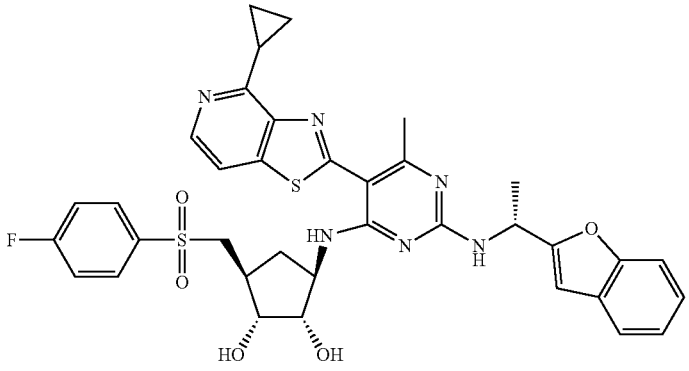
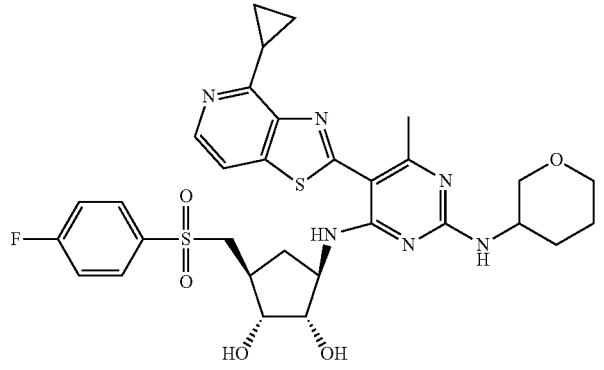
Compd #	Structure	LC-MS or MS $(M + H)^+$
4643		669.7
4644		683.7
4645		715.7
4646		655.7

TABLE IIIA-continued

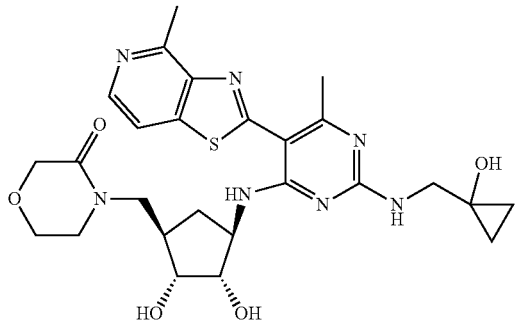
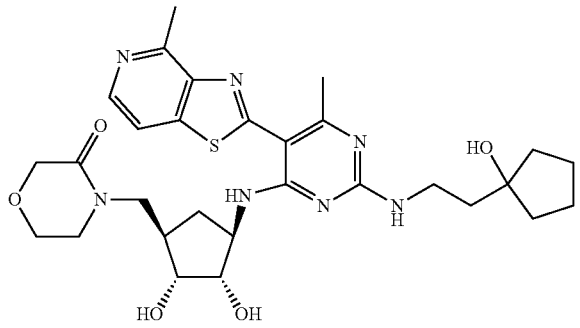
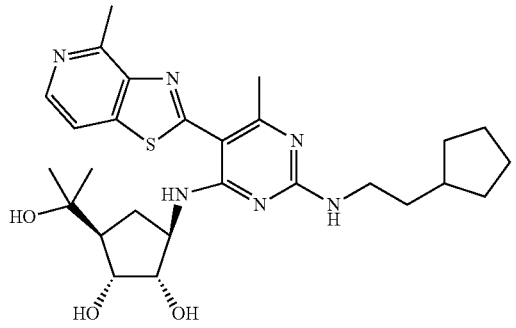
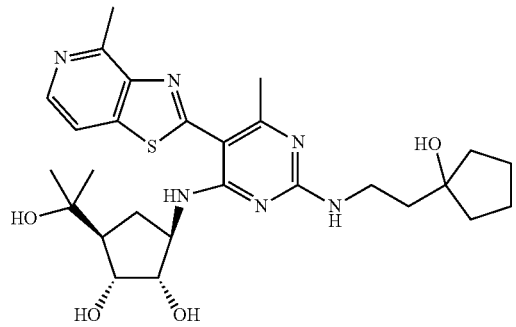
Compd #	Structure	LC-MS or MS $(M + H)^+$
4647		556.7
4648		598.7
4649		527.7
4650		543.7

TABLE IIIA-continued

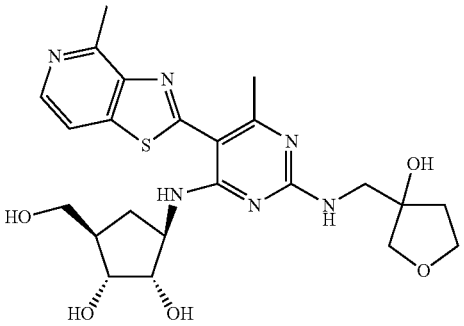
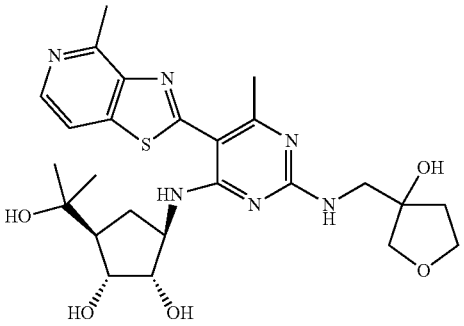
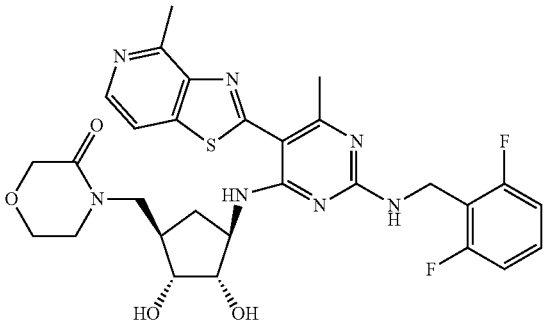
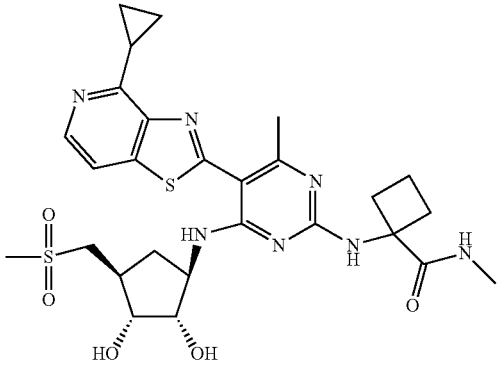
Compd #	Structure	LC-MS or MS $(M + H)^+$
4651		503.7
4652		531.7
4653		612.7
4654		602.7

TABLE IIIA-continued

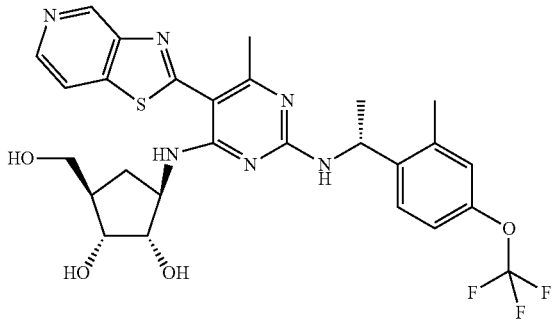
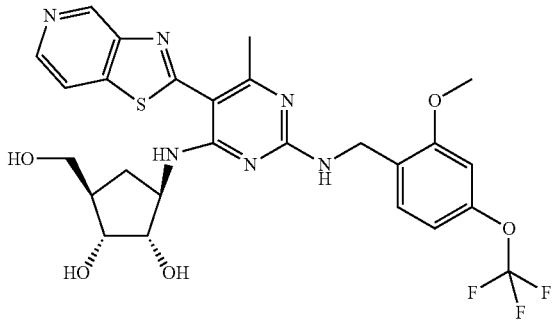
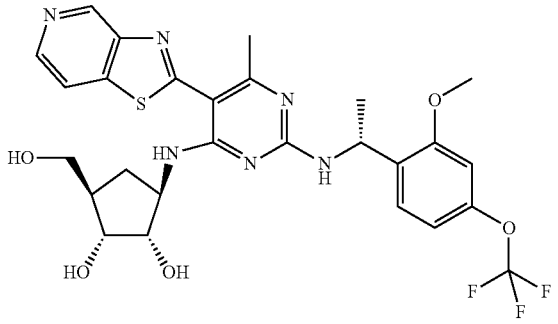
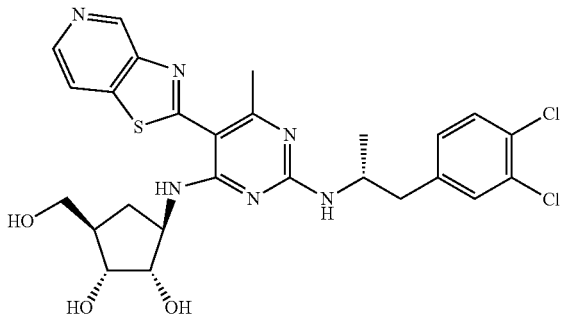
Compd #	Structure	LC-MS or MS $(M + H)^+$
4701		591.1
4702		593.2
4703		607.2
4704		574.9

TABLE IIIA-continued

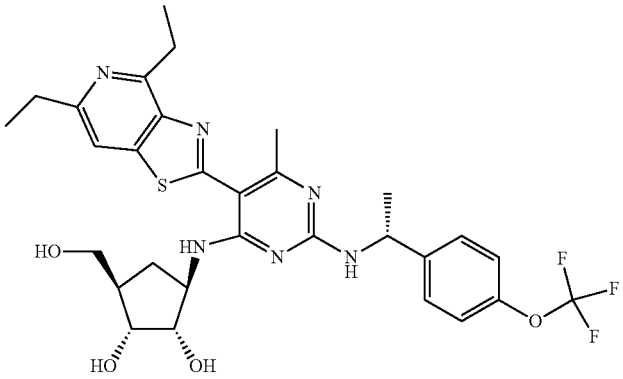
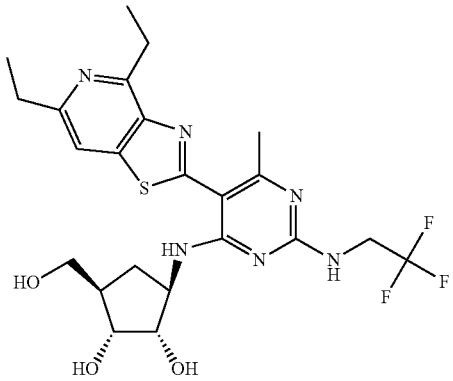
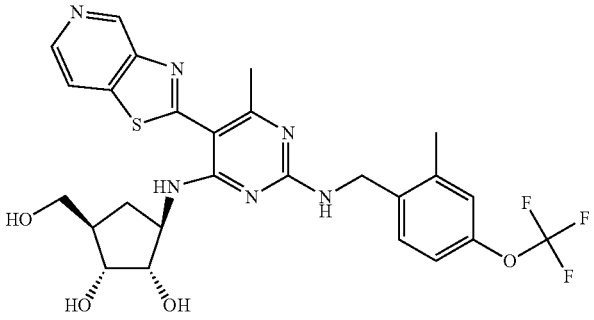
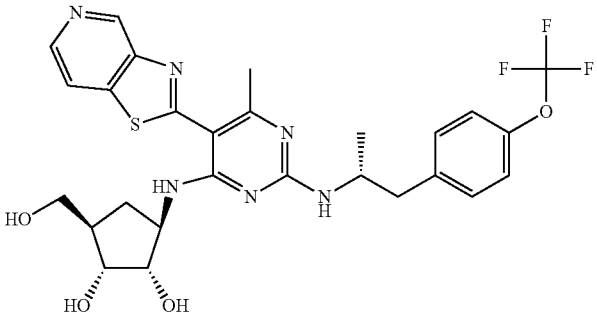
Compd #	Structure	LC-MS or MS $(M + H)^+$
4705		633.2
4706		527.2
4707		577.2
4708		591.5

TABLE IIIA-continued

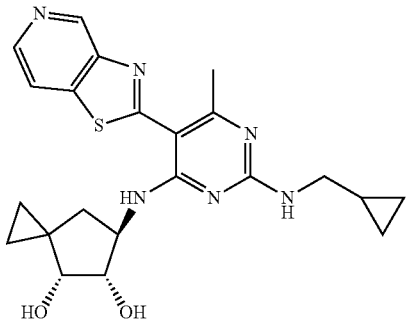
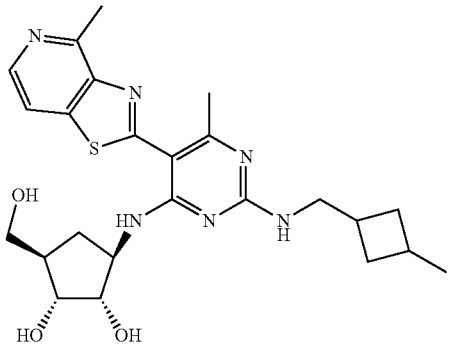
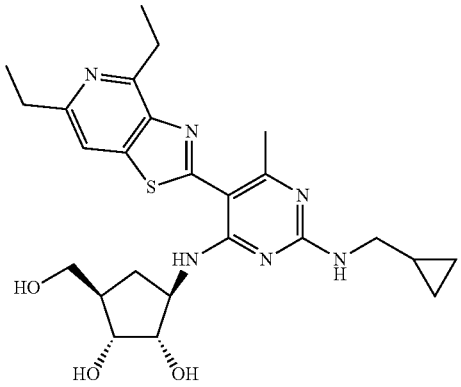
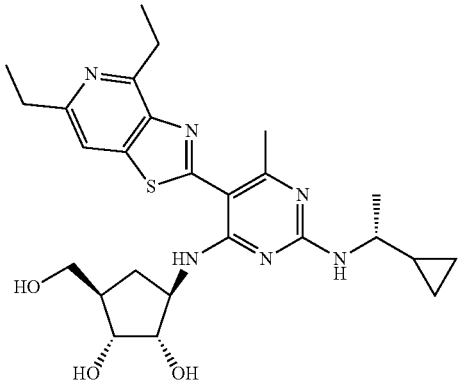
Compd #	Structure	LC-MS or MS $(M + H)^+$
4711		439.1
4712		485.3
4713		499.2
4714		513.2

TABLE IIIA-continued

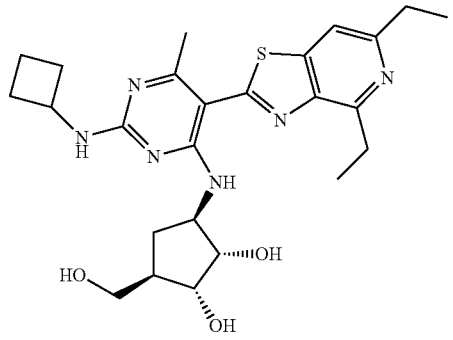
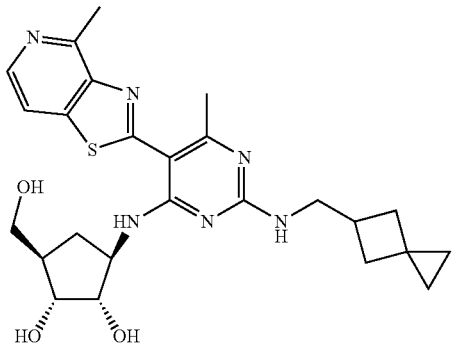
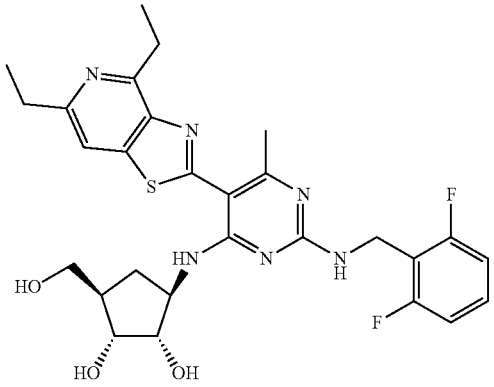
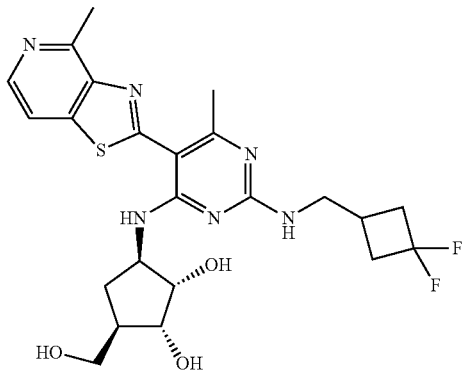
Compd #	Structure	LC-MS or MS $(M + H)^+$
4715		499.7
4716		497.8
4717		571.2
4718		507.3

TABLE IIIA-continued

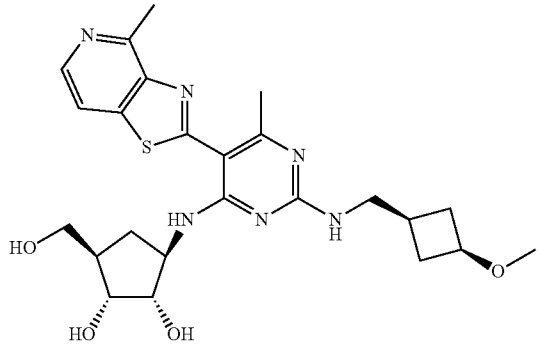
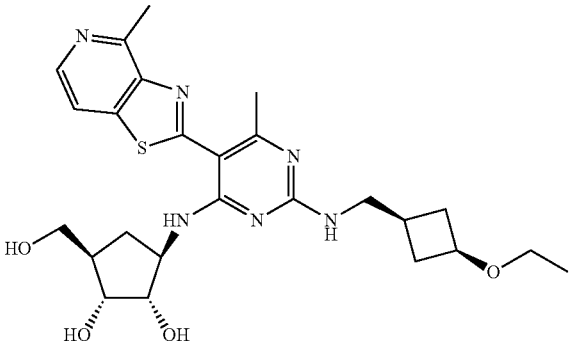
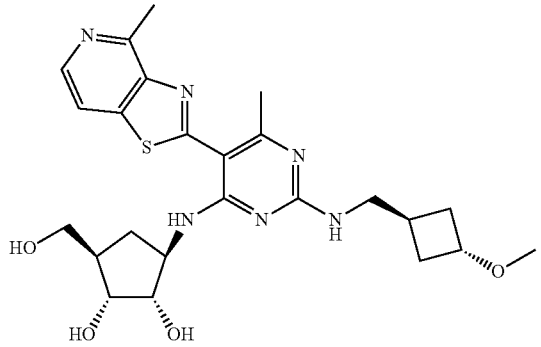
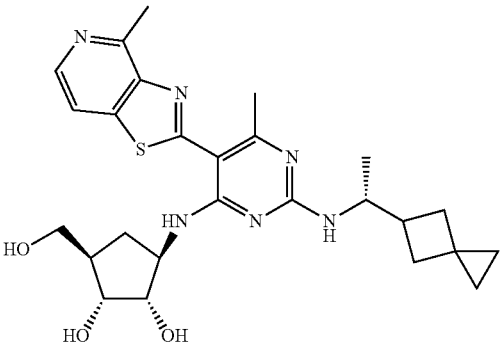
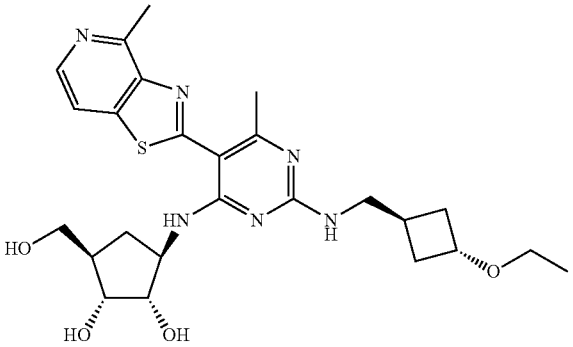
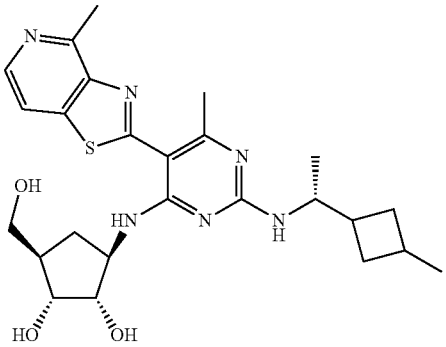
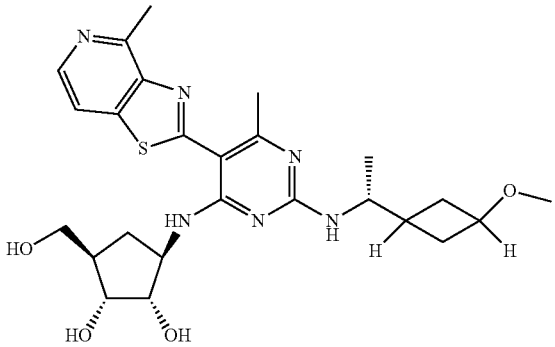
Compd #	Structure	LC-MS or MS $(M + H)^+$
4719		501.2
4721		515.2
4722		501.2
4723		511.2

TABLE IIIA-continued

Compd #	Structure	LC-MS or MS $(M + H)^+$
4724		515.2
4726		499.9
4727		515.2

HCV Replicon assay data for compounds of the invention shown in Table IIIB that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIIB as a falling within the following range: "B"—greater than about 0.5 μM to less than or equal to about 5.0 μM

TABLE IIIB

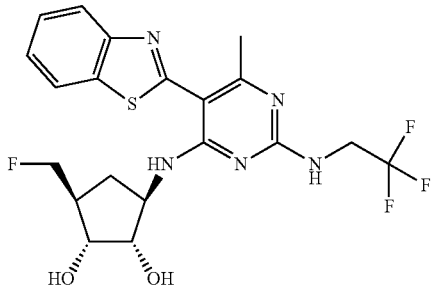
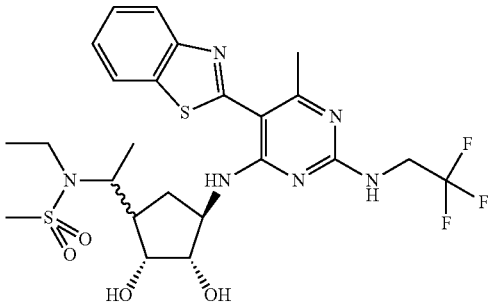
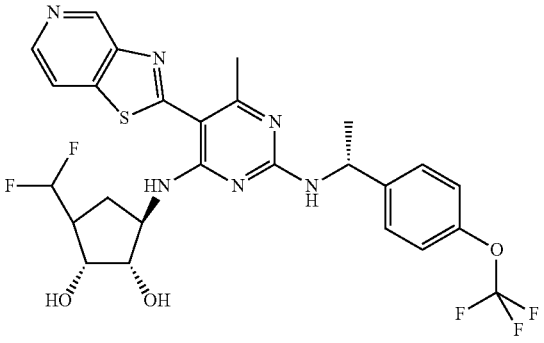
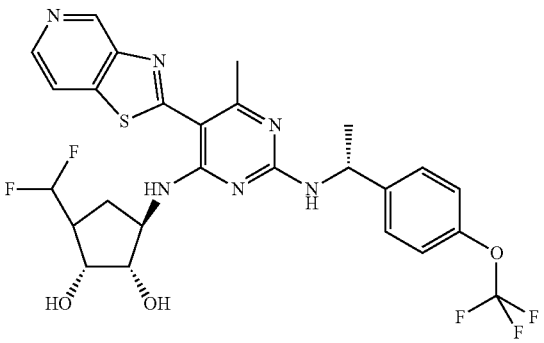
Compd #	Structure	LC-MS or MS $(M + H)^+$
3000		472.3
3003		489.3
3004		597.3
3005		597.3

TABLE IIIB-continued

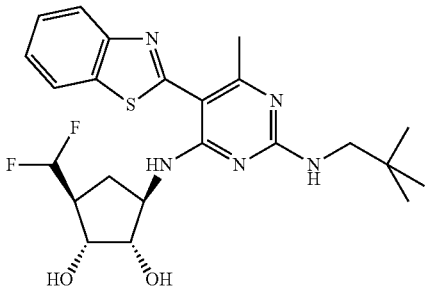
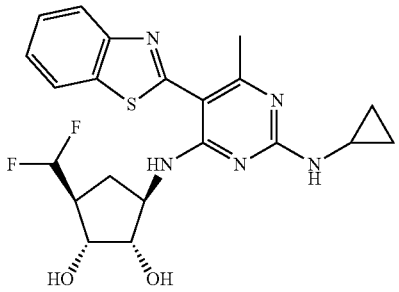
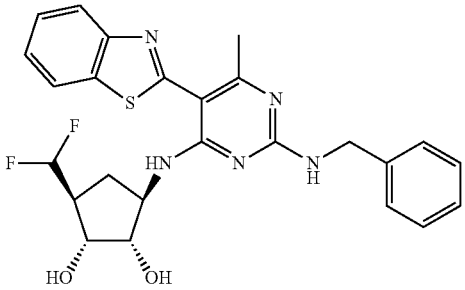
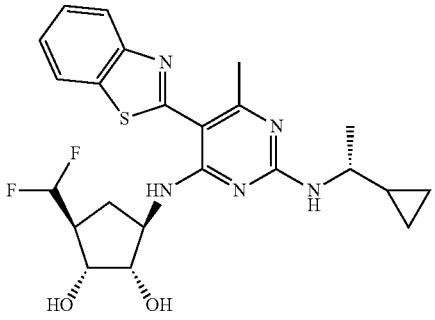
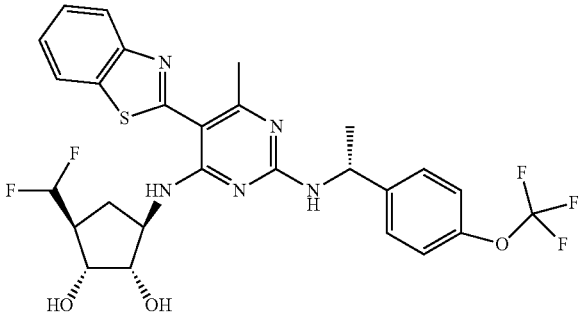
Compd #	Structure	LC-MS or MS $(M + H)^+$
3008		478.3
3010		448.2
3012		498.3
3014		476.3
3015		596.3

TABLE IIIB-continued

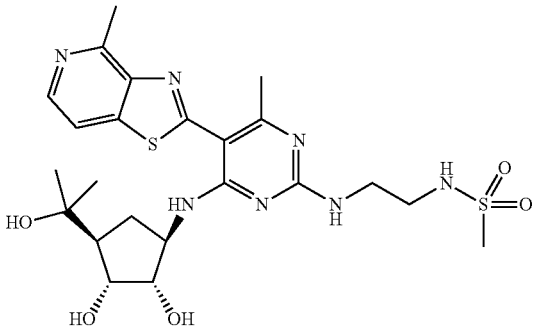
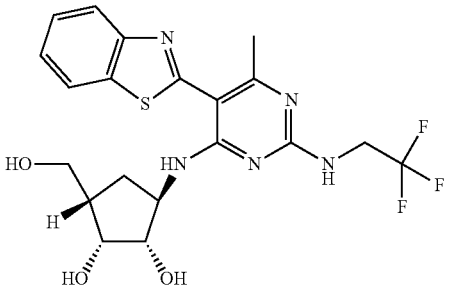
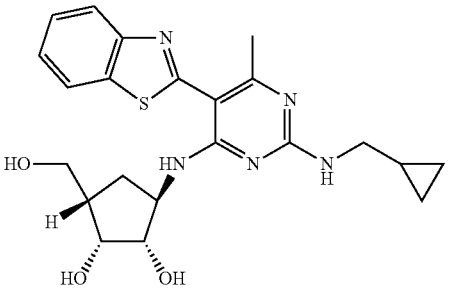
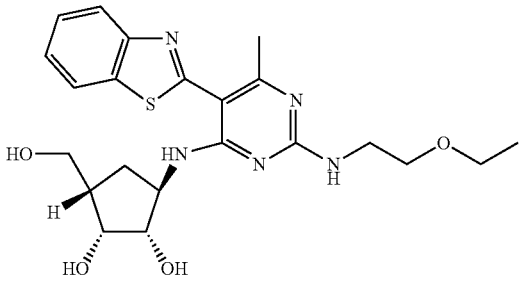
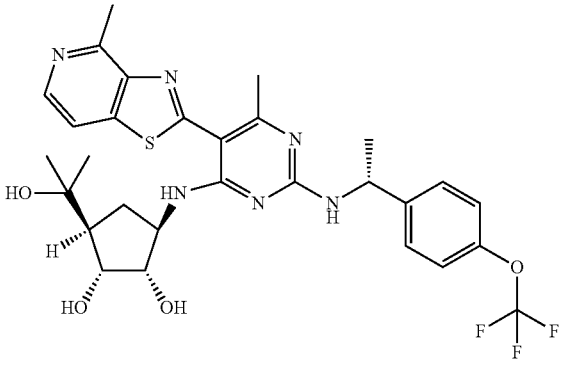
Compd #	Structure	LC-MS or MS $(M + H)^+$
3027		552.3
3101		470.2
3102		442.2
3103		460.2
3110		619.2

TABLE IIIB-continued

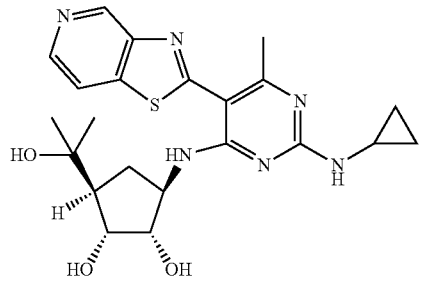
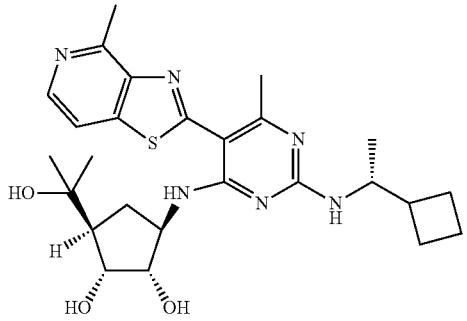
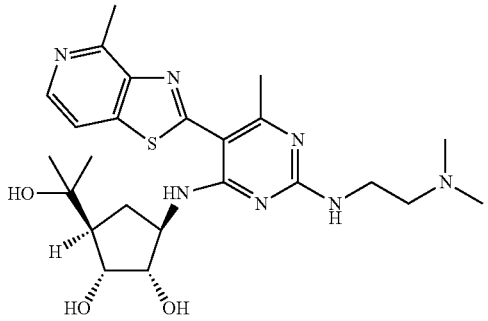
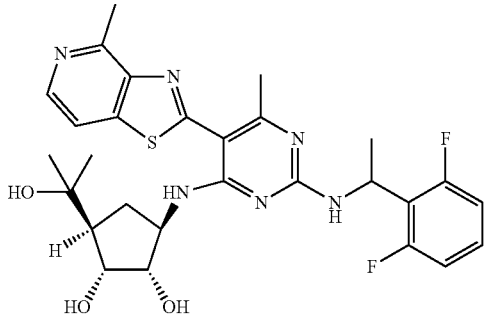
Compd #	Structure	LC-MS or MS $(M + H)^+$
3128		457.2
3140		513.2
3143		502.2
3151		571.2

TABLE IIIB-continued

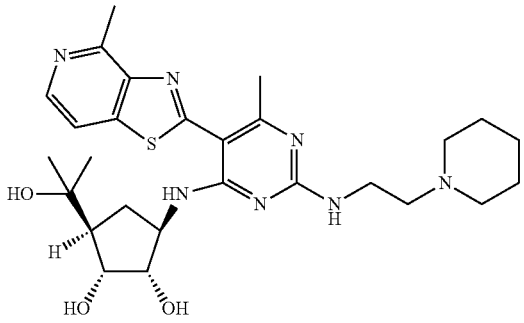
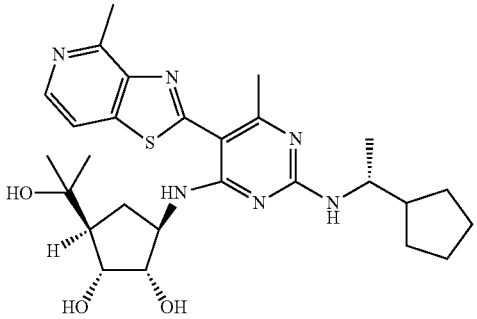
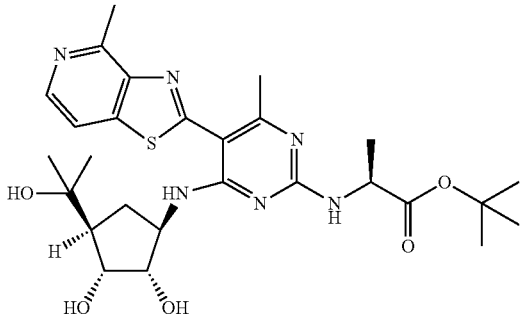
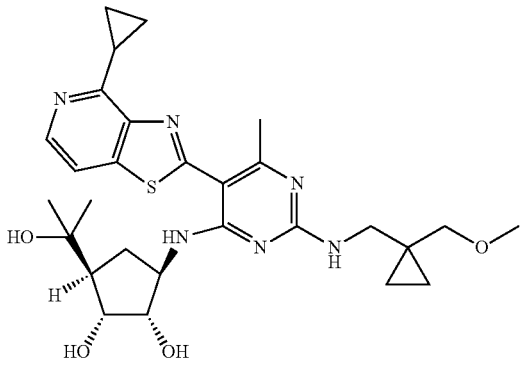
Compd #	Structure	LC-MS or MS $(M + H)^+$
3152		542.2
3173		527.2
3180		559.2
3203		555.2

TABLE IIIB-continued

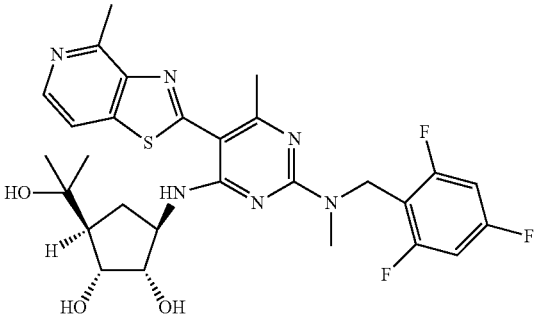
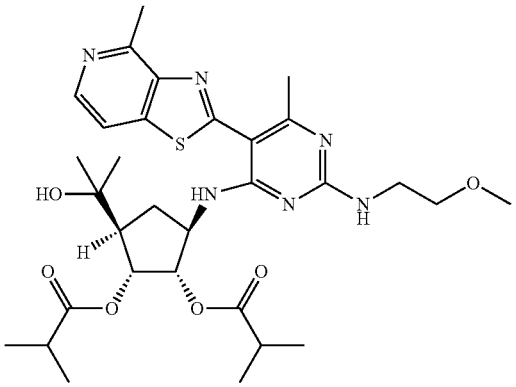
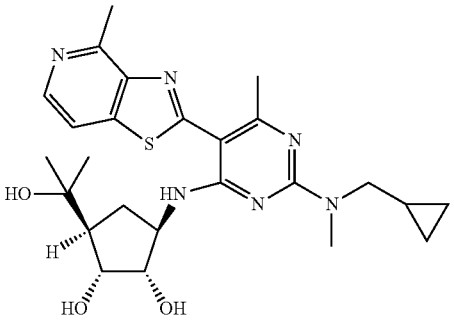
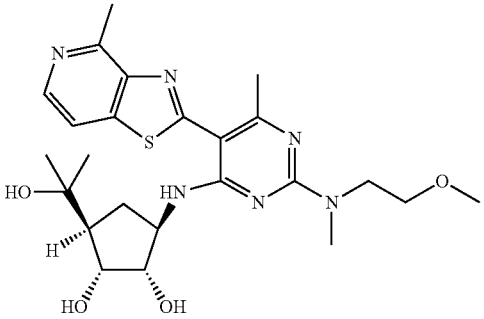
Compd #	Structure	LC-MS or MS $(M + H)^+$
3223		589.2
3228		629.2
3235		499.2
3236		503.2

TABLE IIIB-continued

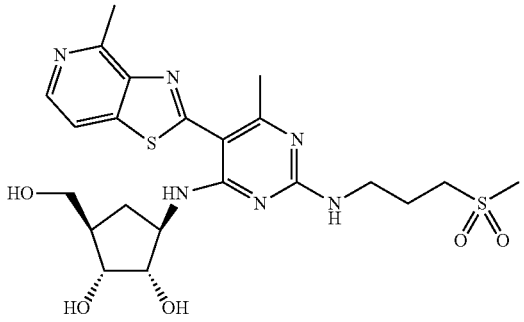
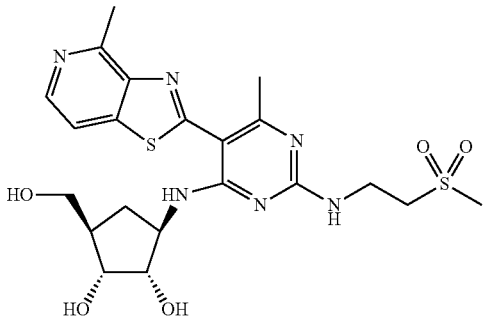
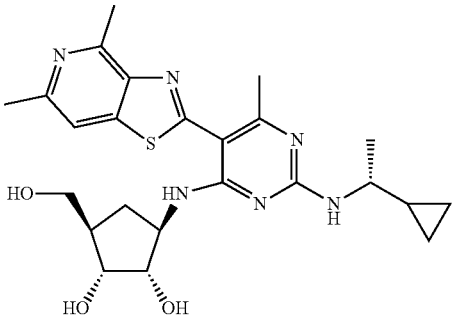
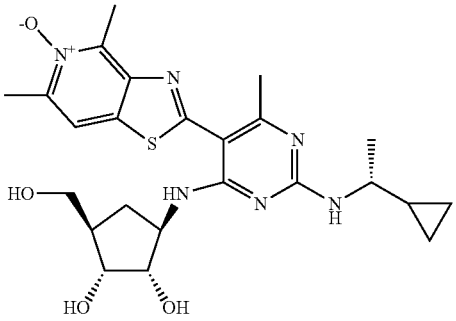
Compd #	Structure	LC-MS or MS $(M + H)^+$
3311		523.1
3312		509.1
3403		485.3
3404		501.2

TABLE IIIB-continued

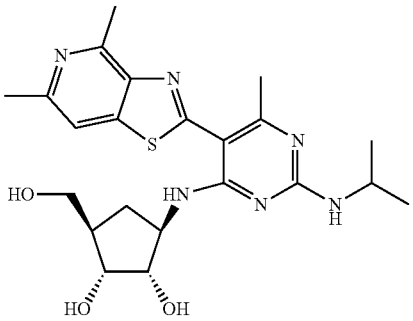
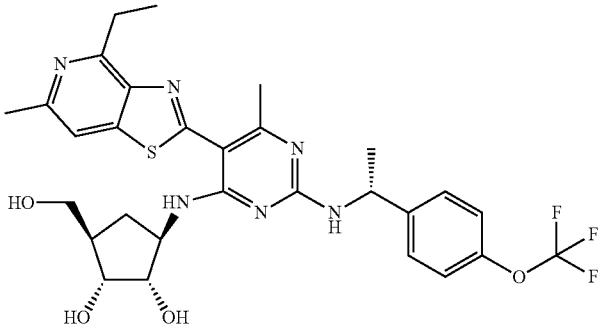
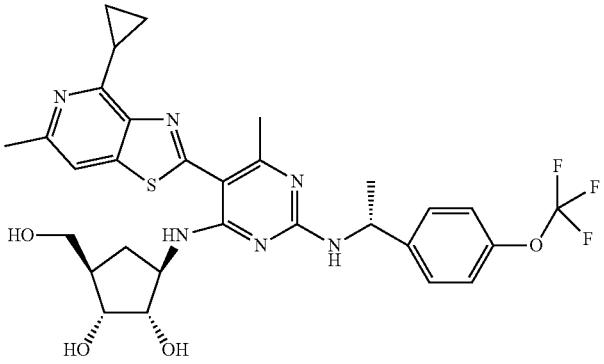
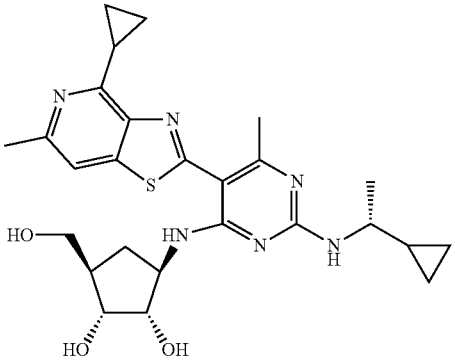
Compd #	Structure	LC-MS or MS $(M + H)^+$
3407		459.2
3410		619.2
3413		631.2
3414		511.2

TABLE IIIB-continued

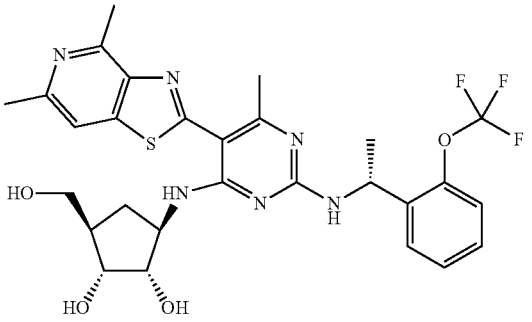
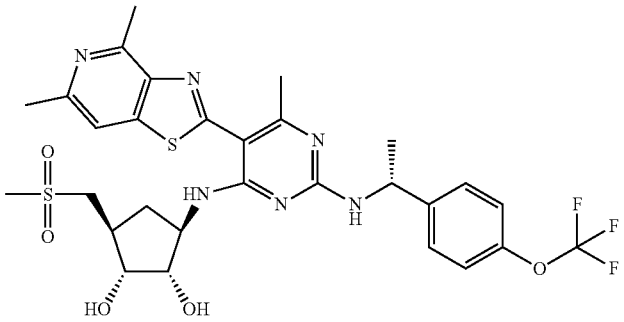
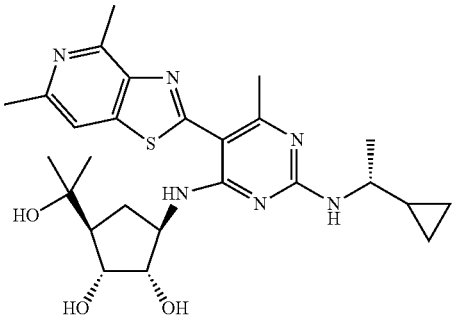
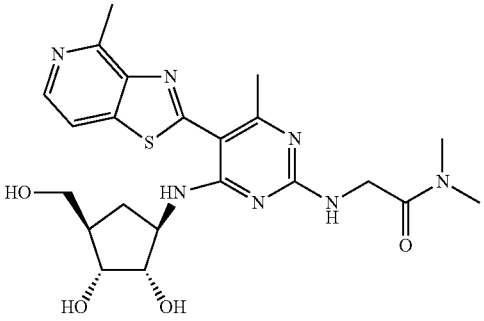
Compd #	Structure	LC-MS or MS $(M + H)^+$
3420		605.2
3422		667.2
3423		513.2
3452		

TABLE IIIB-continued

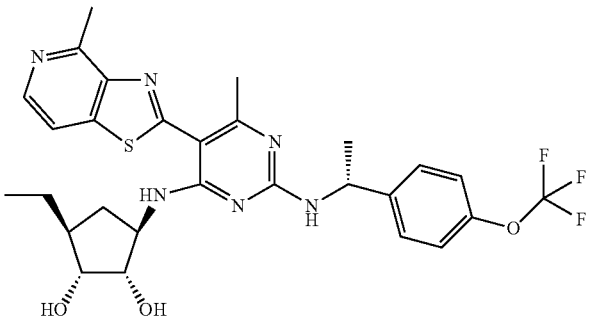
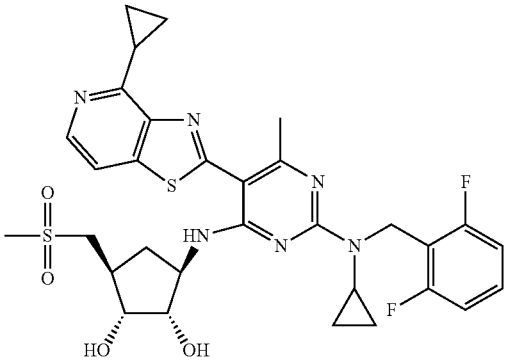
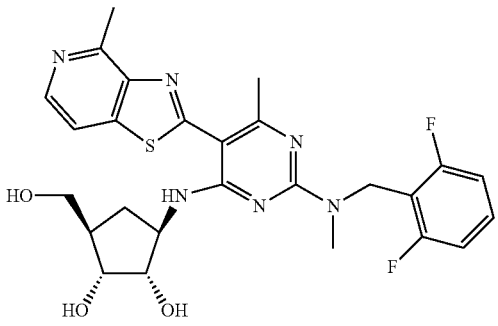
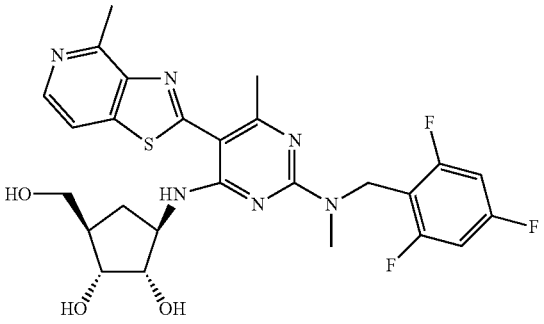
Compd #	Structure	LC-MS or MS $(M + H)^+$
3559		589.4
3595		656.8
3596		543.0
3597		561.0

TABLE IIIB-continued

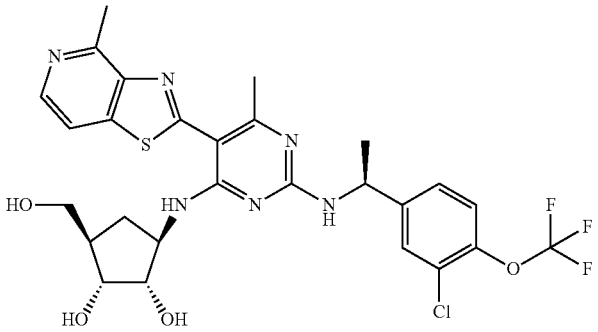
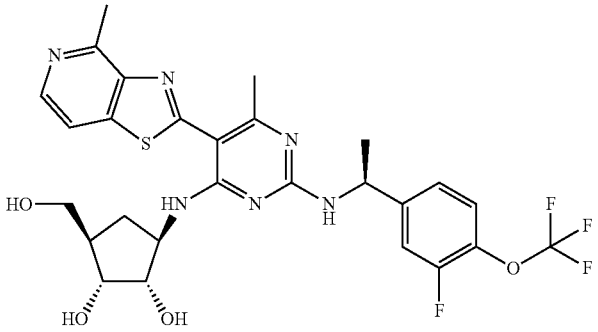
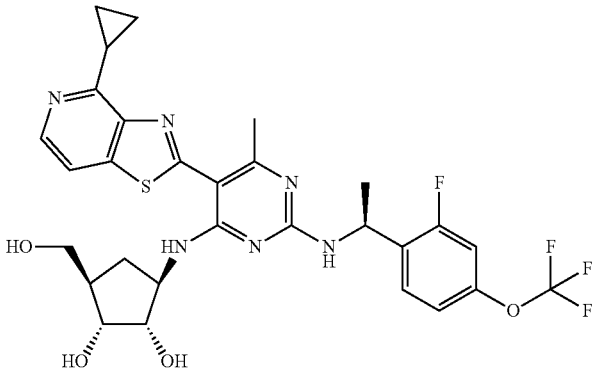
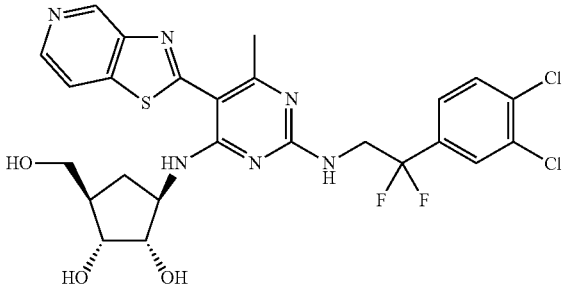
Compd #	Structure	LC-MS or MS $(M + H)^+$
3710		625.3
3713		609.2
3839		635.2
3902		—

TABLE IIIB-continued

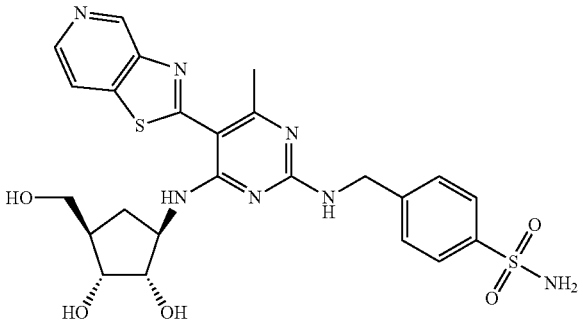
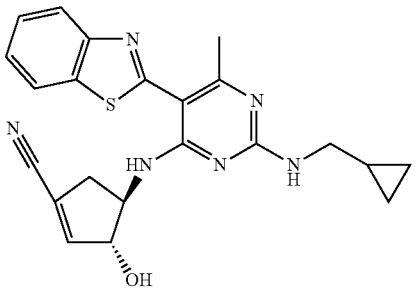
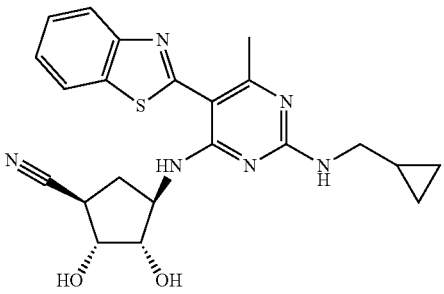
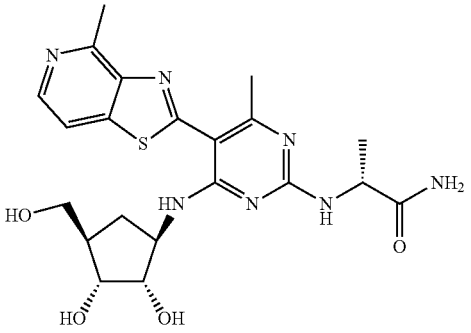
Compd #	Structure	LC-MS or MS $(M + H)^+$
4005		558
4112		419.2
4113		437.2
4118		474.3

TABLE IIIB-continued

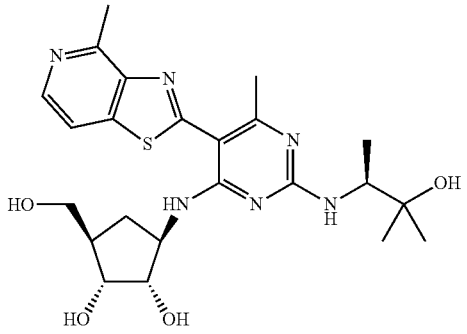
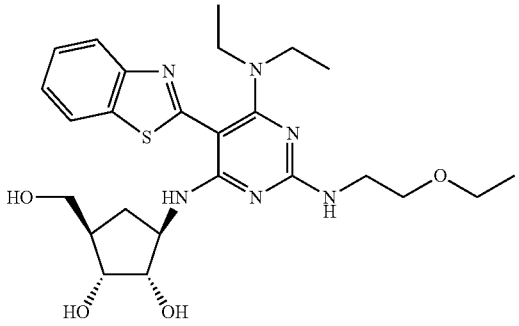
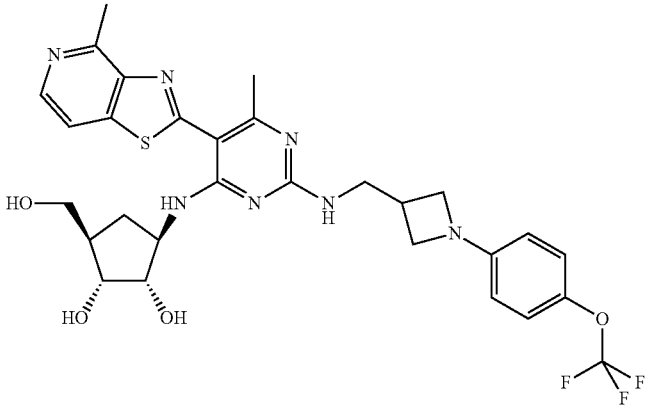
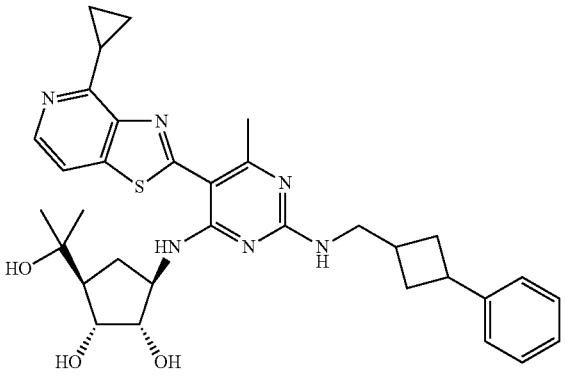
Compd #	Structure	LC-MS or MS $(M + H)^+$
4124		489.3
4201		517
4209		632.3
4214		601.3

TABLE IIIB-continued

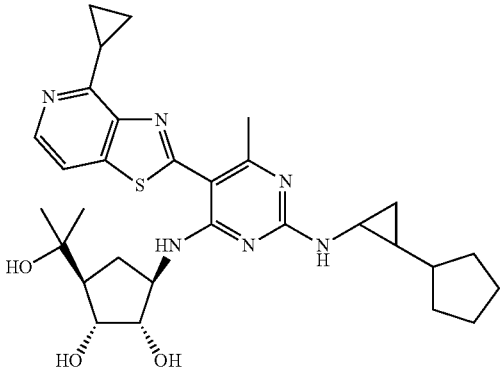
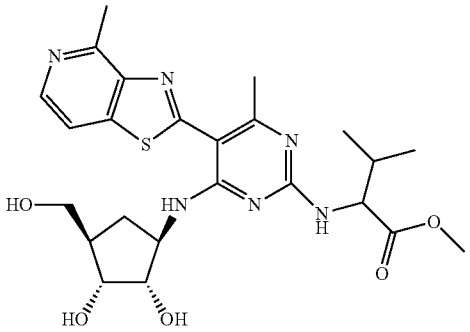
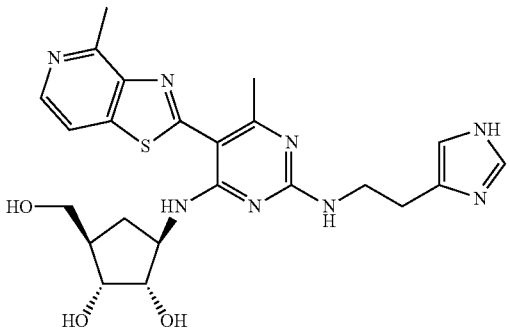
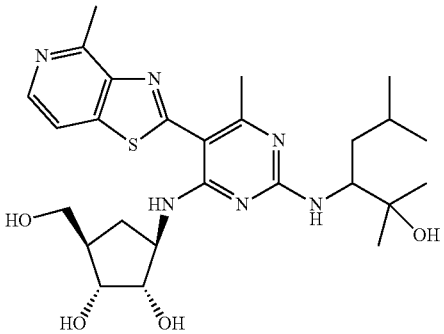
Compd #	Structure	LC-MS or MS $(M + H)^+$
4216		565.3
4218		517.3
4219		497.3
4222		531.3

TABLE IIIB-continued

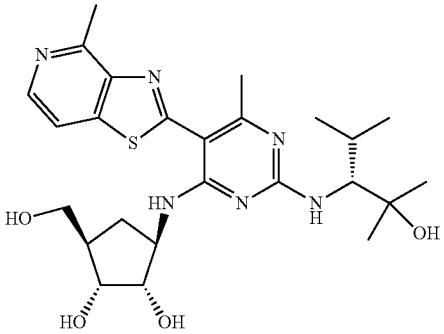
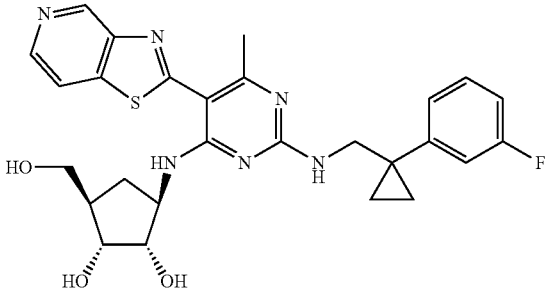
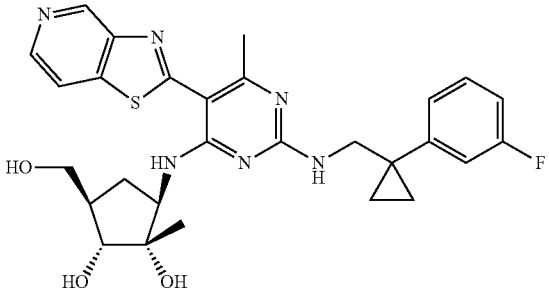
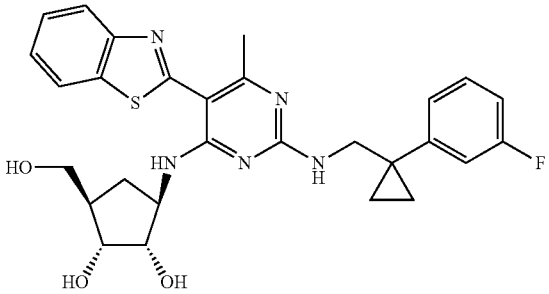
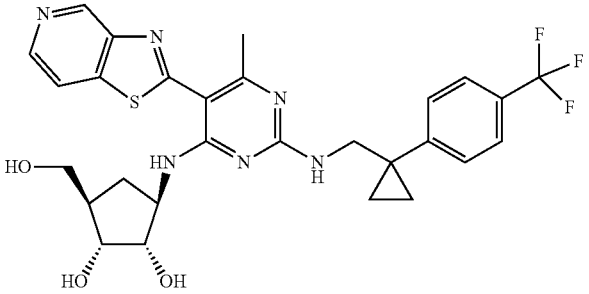
Compd #	Structure	LC-MS or MS $(M + H)^+$
4224		517.3
4315		537.3
4317		551.3
4318		536.2
4408		587.3

TABLE IIIB-continued

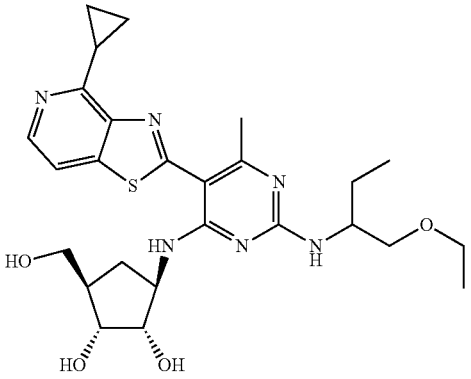
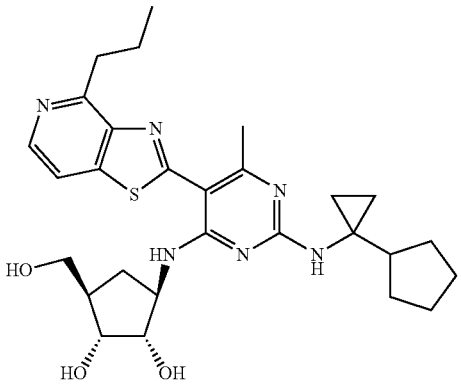
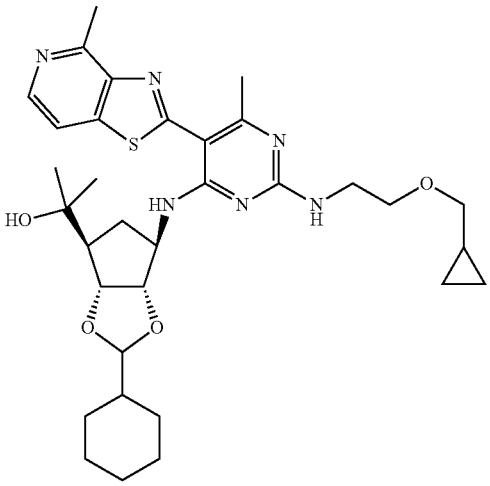
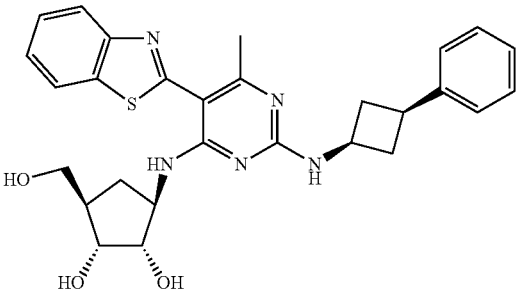
Compd #	Structure	LC-MS or MS $(M + H)^+$
4419		529.3
4430		539.3
4452		623.3
4504		518.3

TABLE IIIB-continued

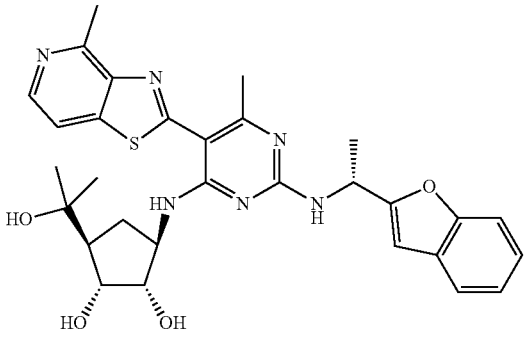
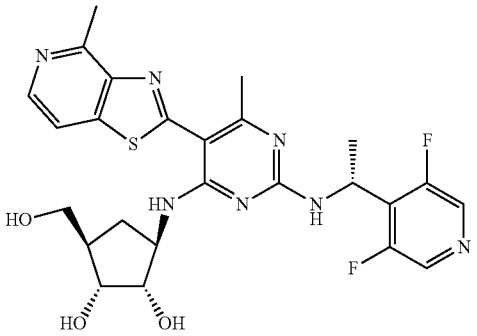
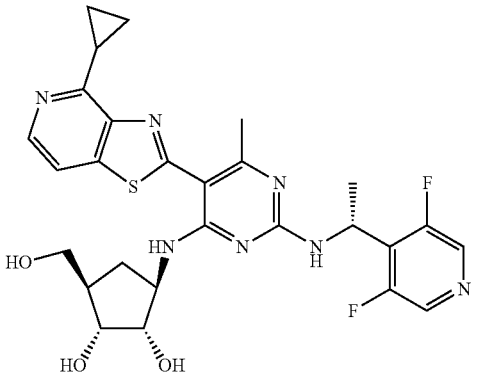
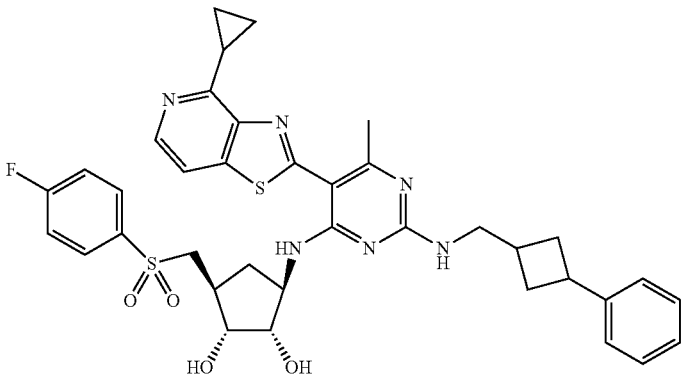
Compd #	Structure	LC-MS or MS $(M + H)^+$
4514		575.2
4525		544.2
4526		570.2
4529		715.3

TABLE IIIB-continued

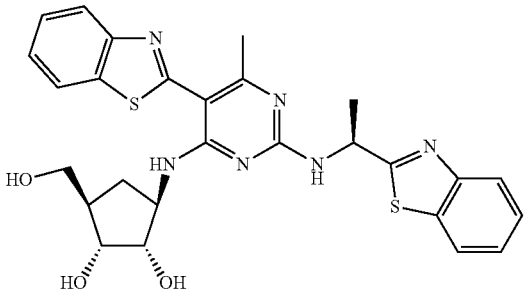
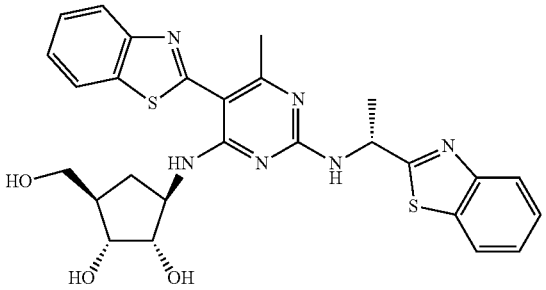
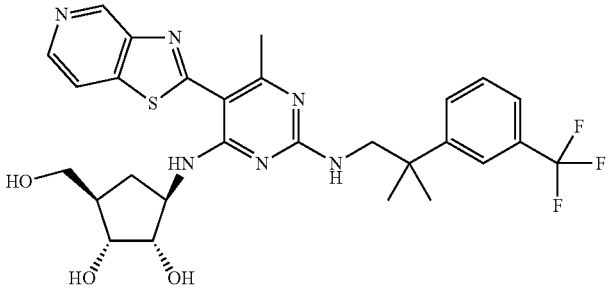
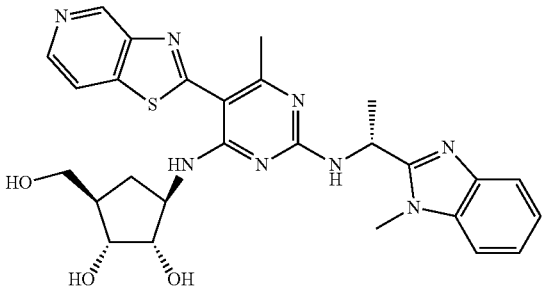
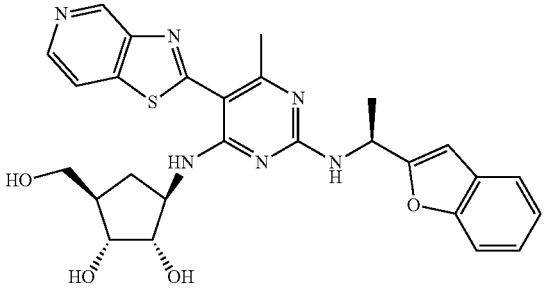
Compd #	Structure	LC-MS or MS $(M + H)^+$
4604		549.3
4605		549.3
4606		589.3
4609		547.3
4610		533.3

TABLE IIIB-continued

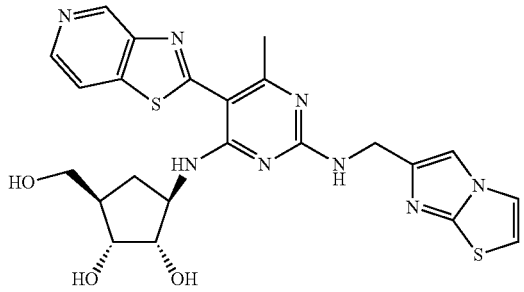
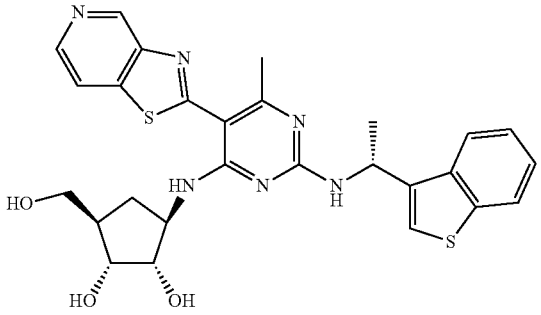
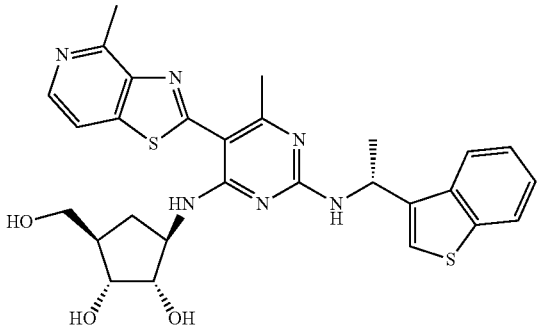
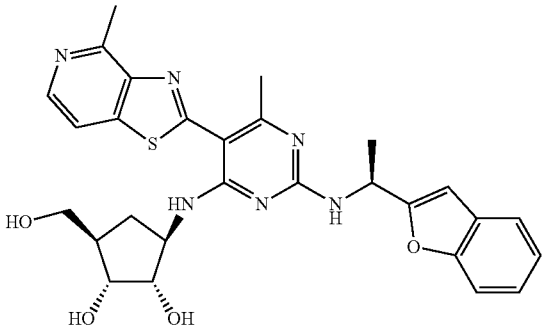
Compd #	Structure	LC-MS or MS $(M + H)^+$
4612		525.3
4613		549.3
4617		563.7
4620		547.3

TABLE IIIB-continued

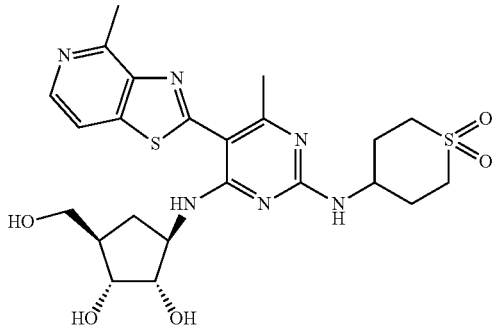
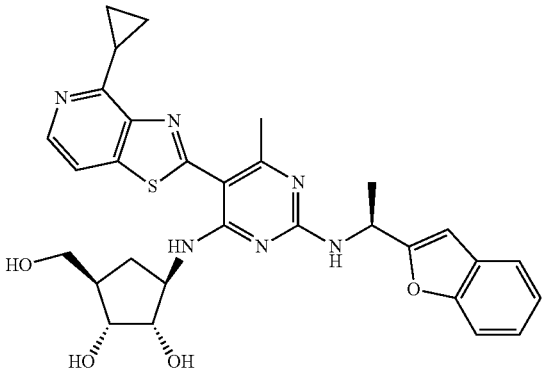
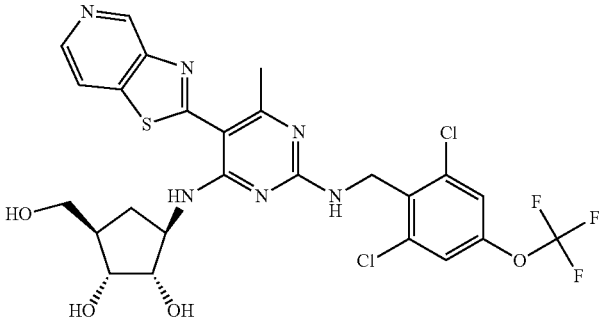
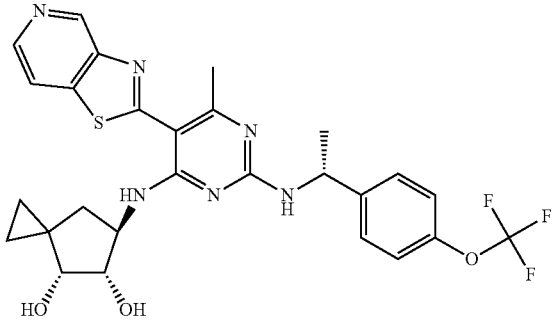
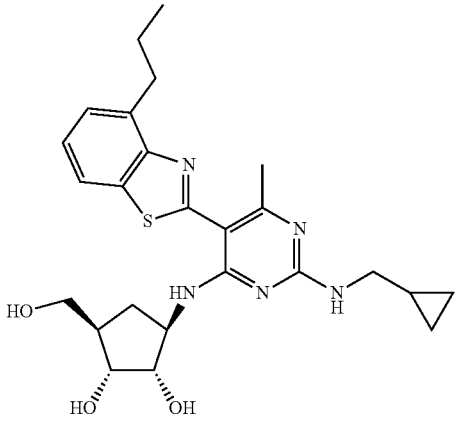
Compd #	Structure	LC-MS or MS $(M + H)^+$
4622		535.3
4630		573.7
4709		631.1
4710		573.2

TABLE IIIB-continued

Compd #	Structure	LC-MS or MS $(M + H)^+$
4720		484.2

HCV Replicon assay data for compounds of the invention shown in Table IIIC that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIIC as a falling within the following range: "C"—greater than about 5.0 μM to less than or equal to about 25 μM

TABLE IIIC

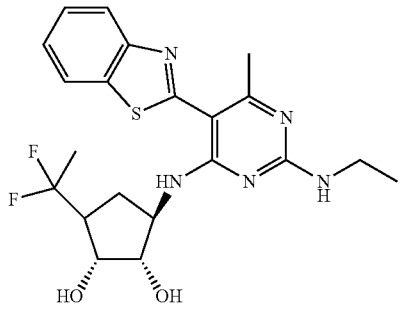
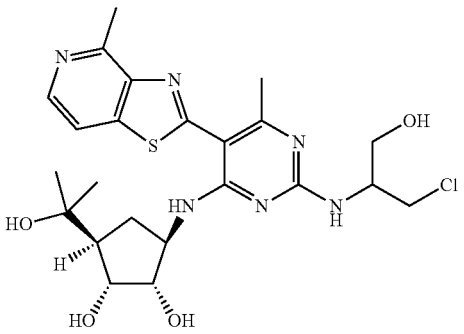
Compd #	Structure	LC-MS or MS $(M + H)^+$
3002		450.2
3172		523.2

TABLE IIIC-continued

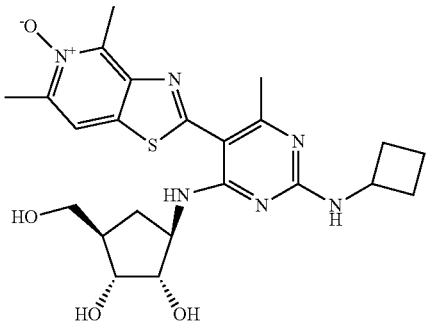
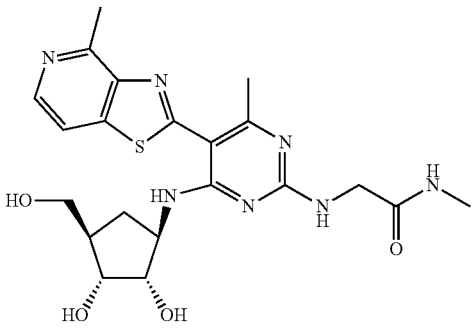
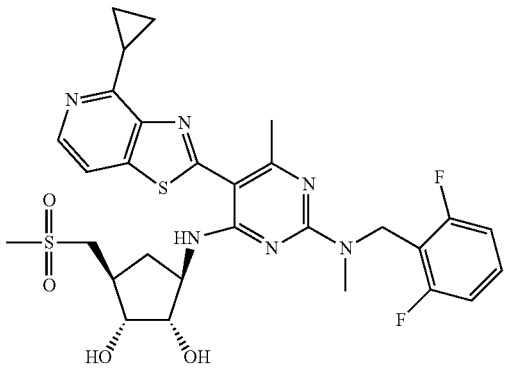
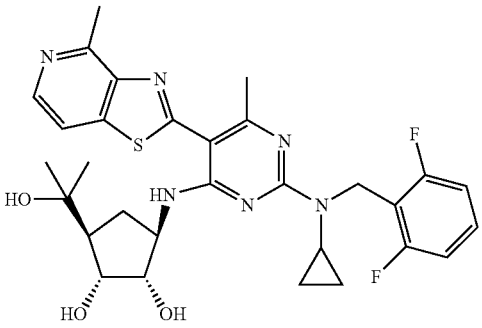
Compd #	Structure	LC-MS or MS $(M + H)^+$
3406		487.2
3429		474.2
3599		631.0
3601		597.0

TABLE IIIC-continued

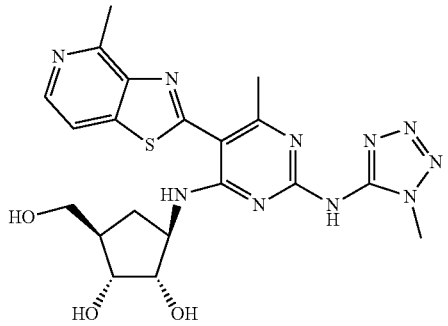
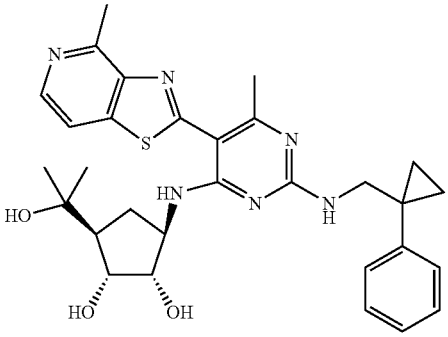
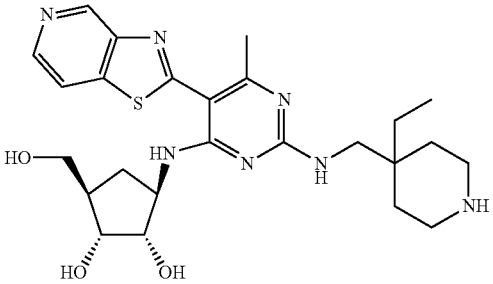
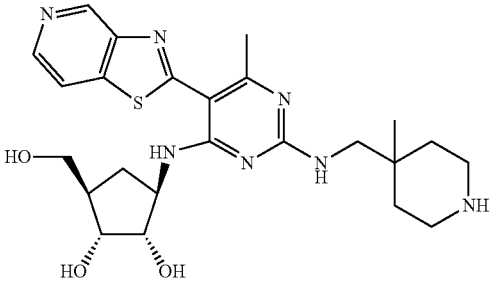
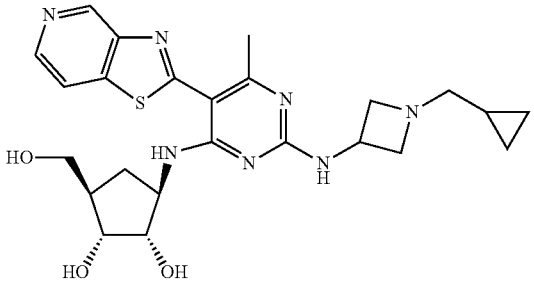
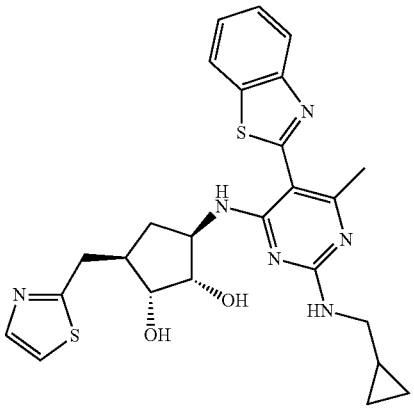
Compd #	Structure	LC-MS or MS $(M + H)^+$
4011		485
4226		561.3
4402		514.3
4403		500.3
4501		498.3

TABLE IIIC-continued

Compd #	Structure	LC-MS or MS $(M + H)^+$
4725		509.3

HCV Replicon assay data for compounds of the invention shown in Table IIID that were tested were obtained using the above method. Calculated EC90 values are reported for each compound in Table IIID as falling within the following range: "D"—greater than about 25.0 μM

TABLE IIID

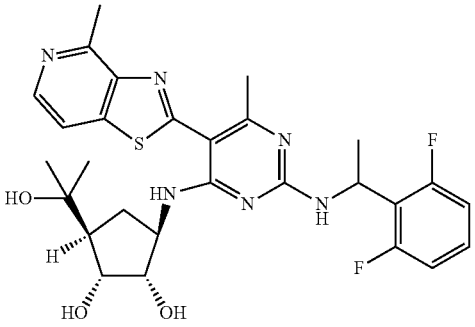
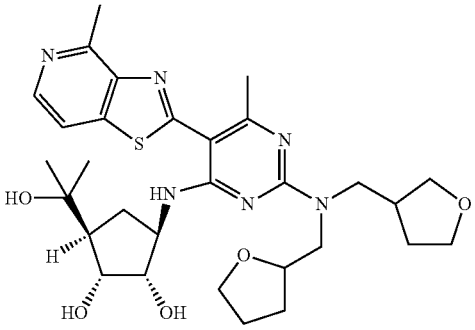
Compd #	Structure	LC-MS or MS $(M + H)^+$
3150		571.2
3196		599.2

TABLE IIID-continued

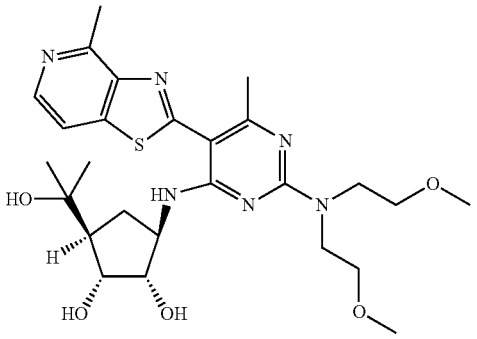
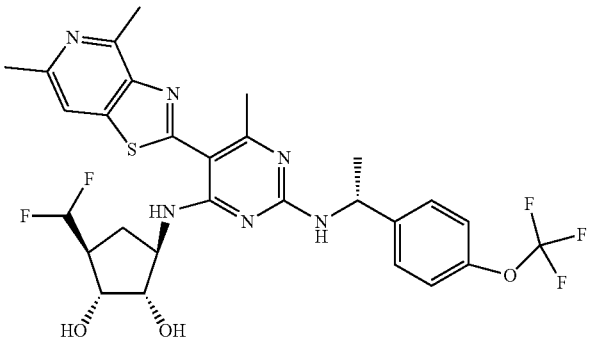
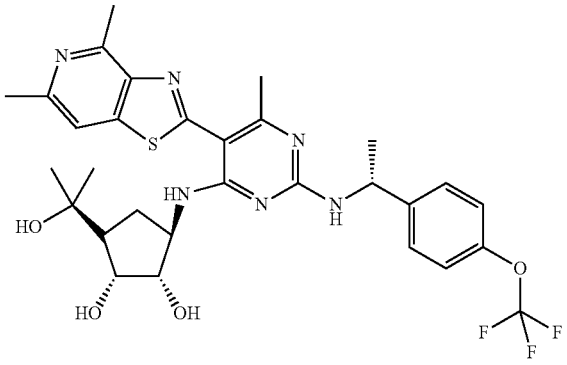
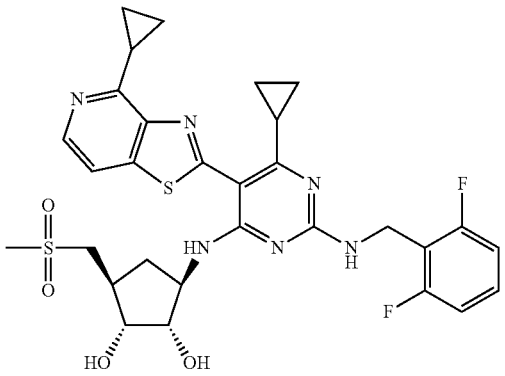
Compd #	Structure	LC-MS or MS $(M + H)^+$
3237		547.2
3409		625.2
3424		633.2
3588		643.0

TABLE IIID-continued

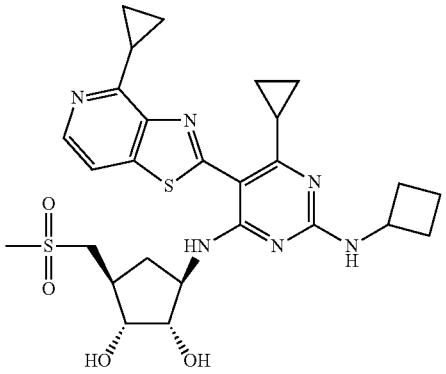
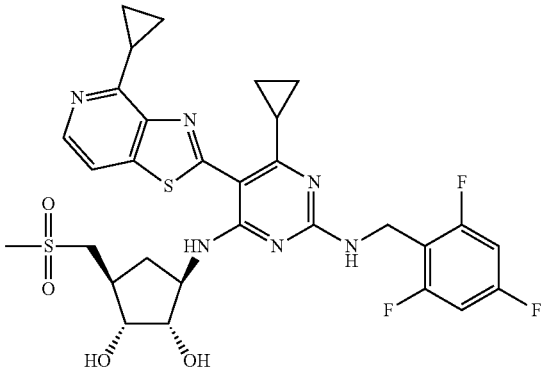
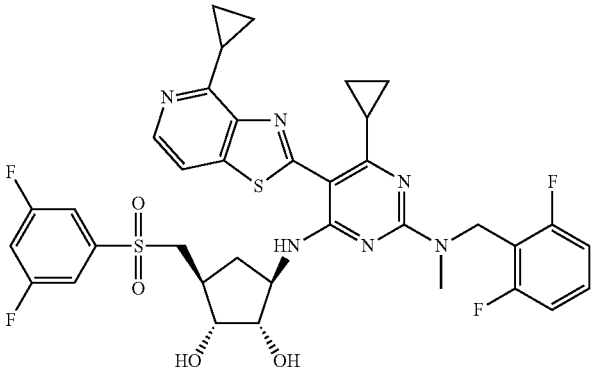
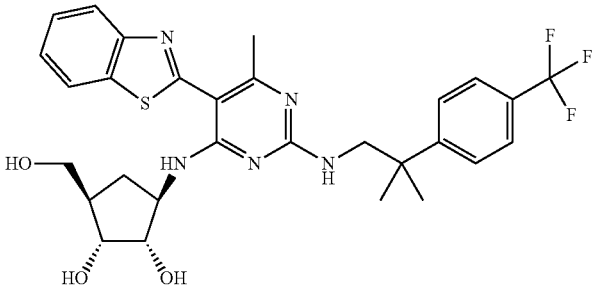
Compd #	Structure	LC-MS or MS $(M + H)^+$
3589		571.0
3590		661.0
3598		702.8
3805		588.2

TABLE IIID-continued

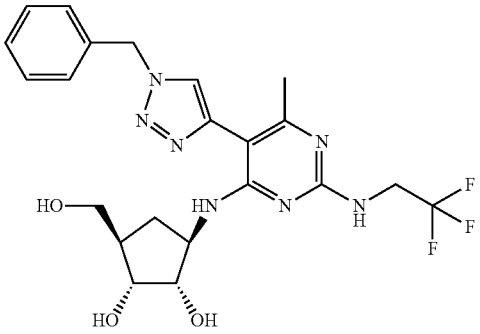
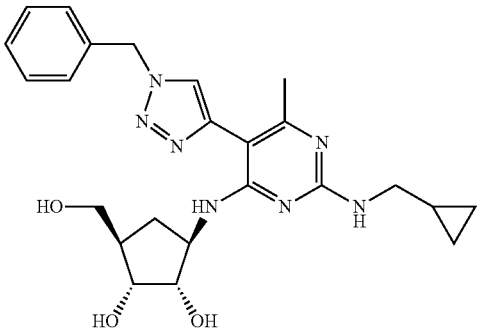
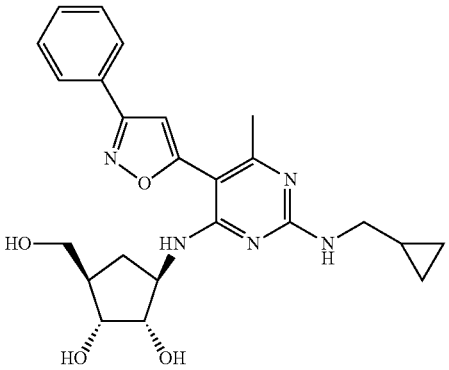
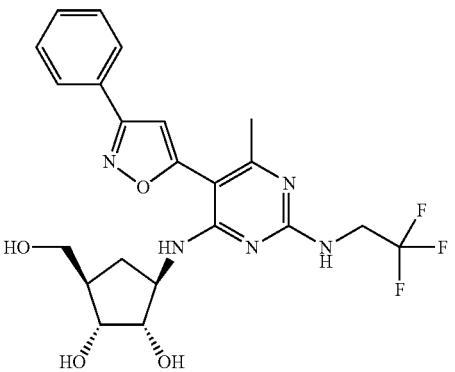
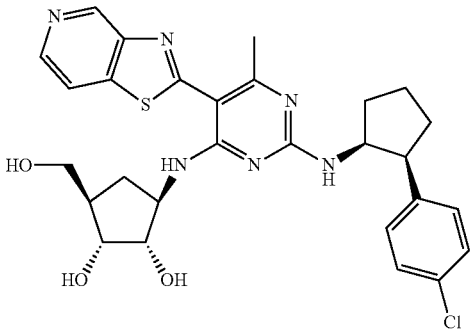
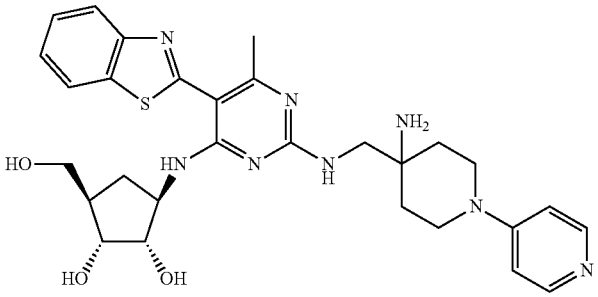
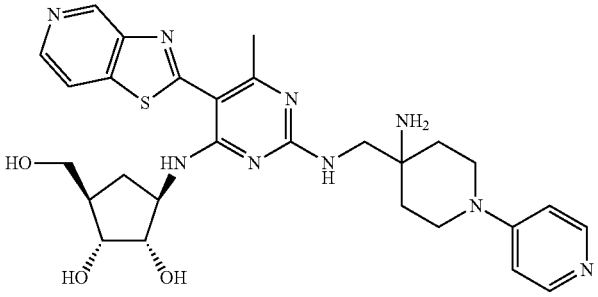
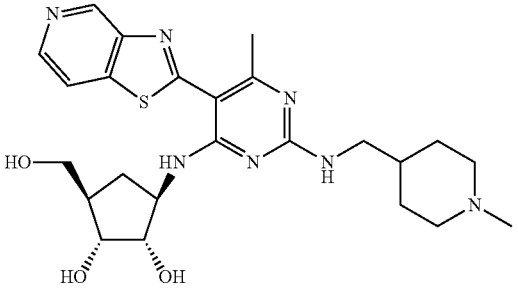
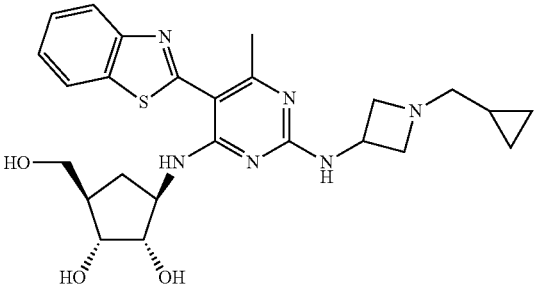
Compd #	Structure	LC-MS or MS $(M + H)^+$
4101		494.3
4102		466.3
4103		452.2
4104		480.3

TABLE IIID-continued

Compd #	Structure	LC-MS or MS $(M + H)^+$
4108		567.3
4110		577.3
4111		578.3
4401		500.3
4502		497.2

HCV Replicon assay data for compounds of the invention shown in Table IIIE that were tested were obtained using the above method. Calculated EC50 values are reported for each compound in Table IIIE as falling within the following range: "E"—less than or equal to about 0.5 μM

TABLE IIIE

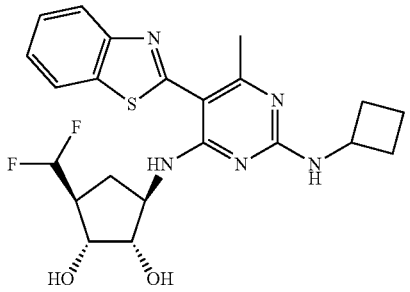
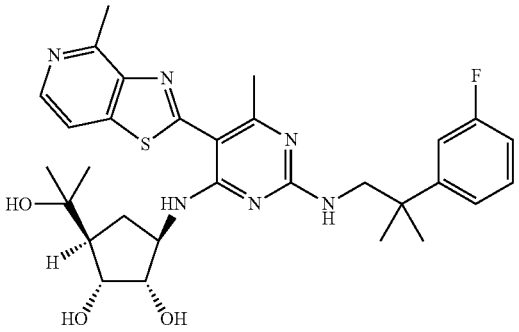
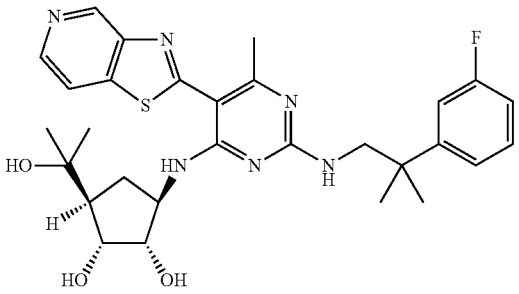
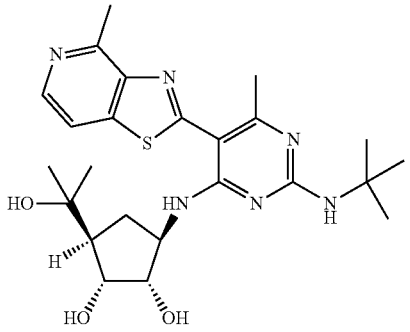
Compd #	Structure	LC-MS or MS $(M + H)^+$
3009		462.3
3124		581.2
3131		567.2
3134		487.2

TABLE IIIE-continued

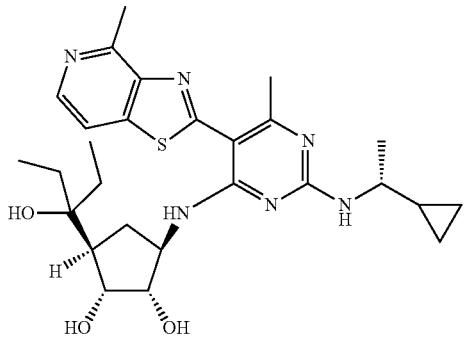
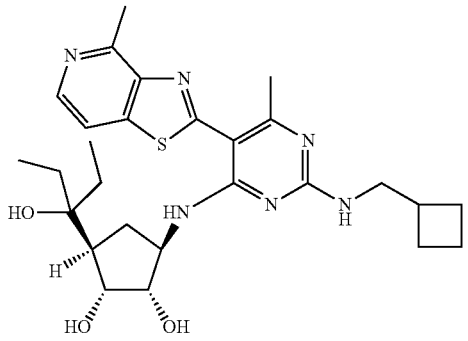
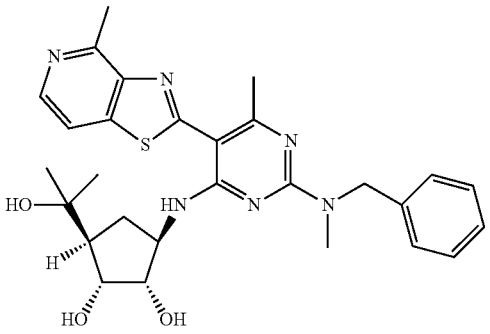
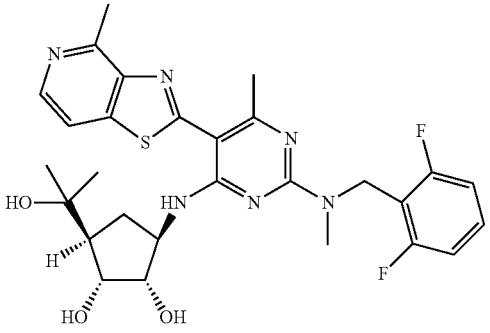
Compd #	Structure	LC-MS or MS $(M + H)^+$
3184		527.2
3221		527.2
3234		535.2
3238		571.2

TABLE IIIE-continued

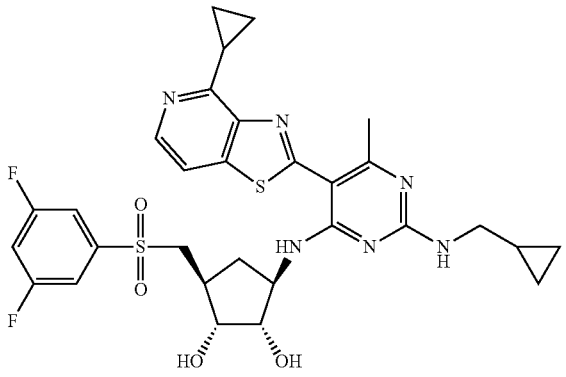
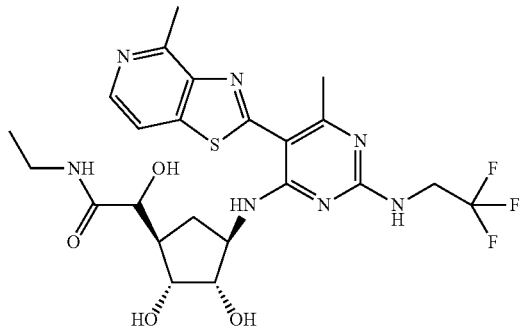
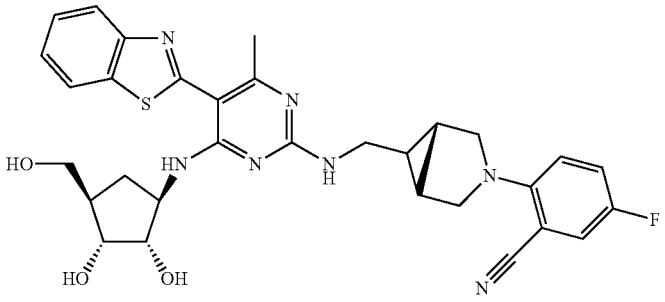
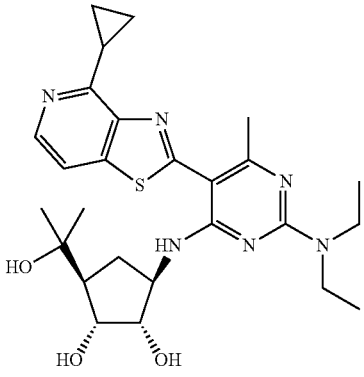
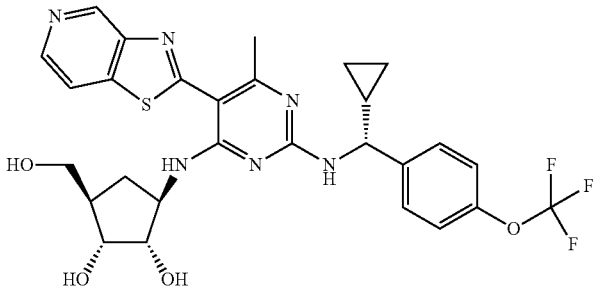
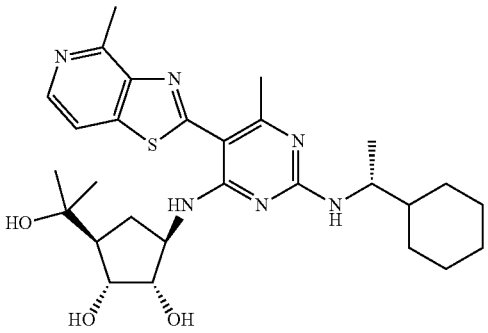
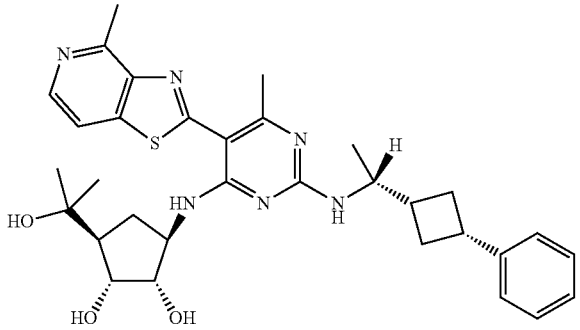
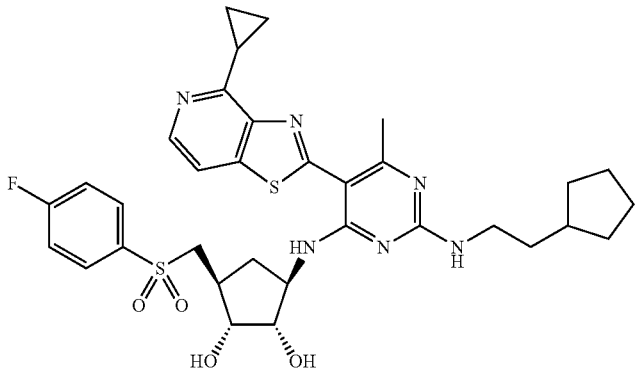
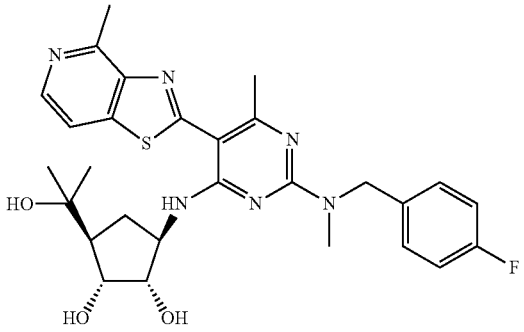
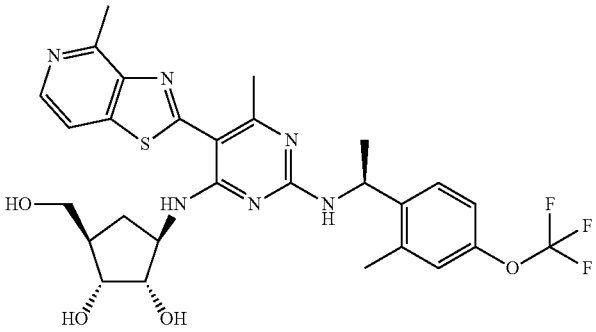
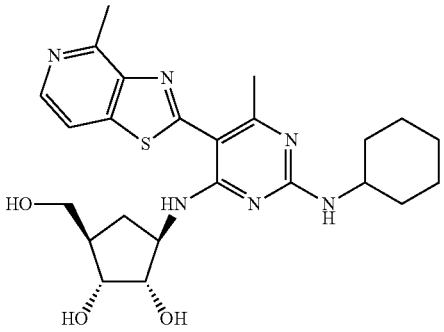
Compd #	Structure	LC-MS or MS $(M + H)^+$
3572		643.1
4022		556
4202		602.3
4215		513.3

TABLE IIIE-continued

Compd #	Structure	LC-MS or MS $(M + H)^+$
4313		603.3
4423		541.3
4519		589.3
4528		667.2

HCV Replicon assay data for compounds of the invention shown in Table IIIF that were tested were obtained using the above method. Calculated EC50 values are reported for each compound in Table IIIF as falling within the following range: "F"—greater than about 0.5 μM to less than or equal to about 5 μM.

TABLE IIIF

Compd #	Structure	LC-MS or MS $(M + H)^+$
3232		553.2
3716		605.3
4314		470.3

HCV Replicon assay data for compounds of the invention shown in Table IV were obtained using the above method.

Calculated EC90 values are reported for selected representative compounds shown in Table IV are as follows:

TABLE IV

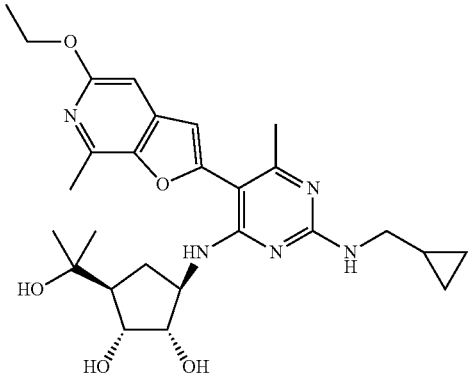
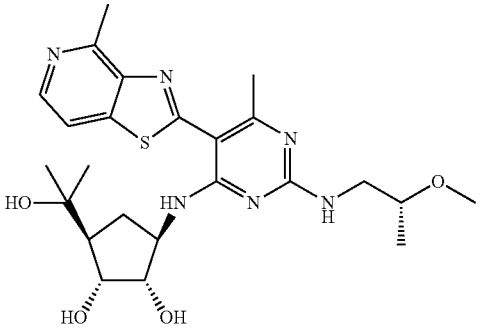
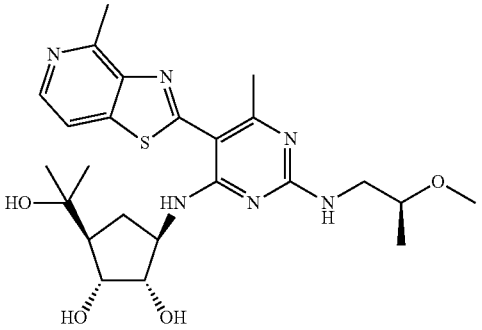
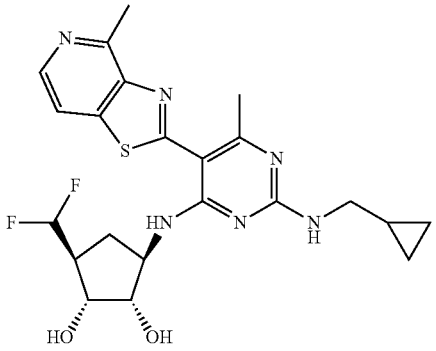
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
2511		0.13	512.3
3030		0.104	503.3
3031		0.104	503.3
3036		0.044	477.3

TABLE IV-continued

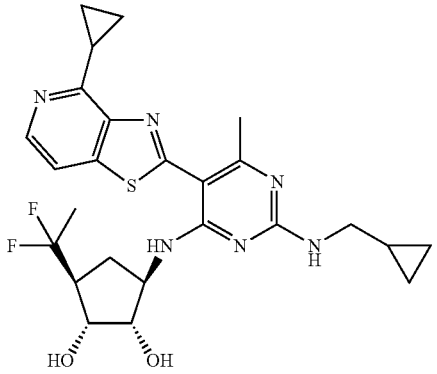
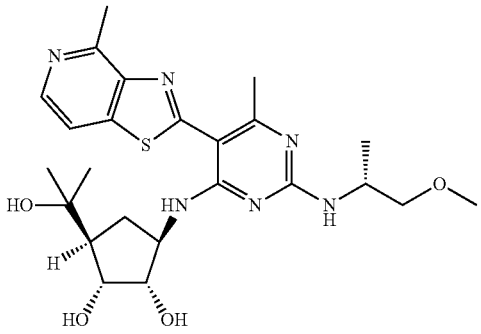
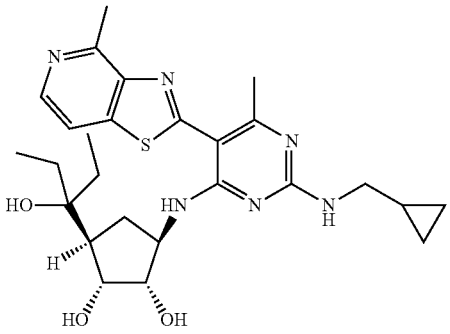
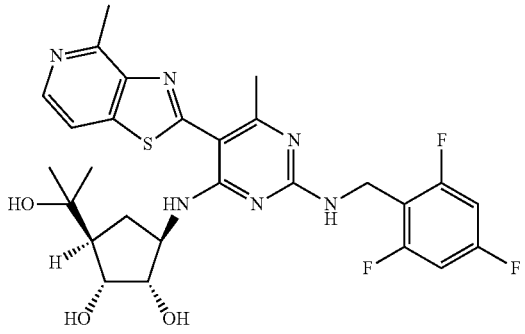
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
3056		0.007	517.3
3137		0.118	503.2
3182		0.068	513.2
3188		0.021	575.2

TABLE IV-continued

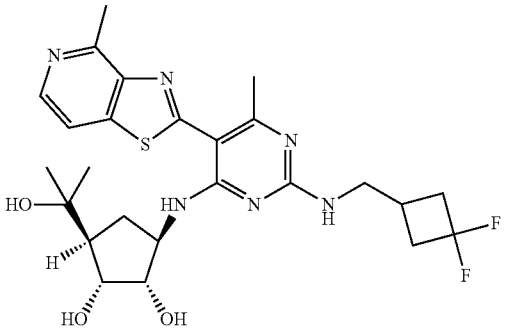
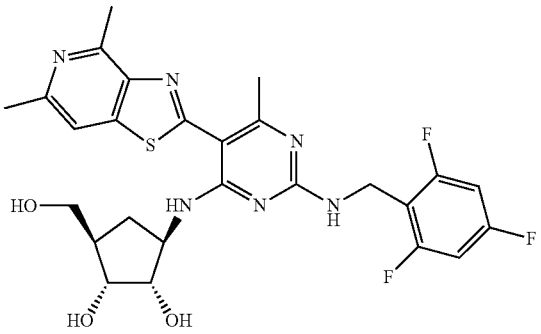
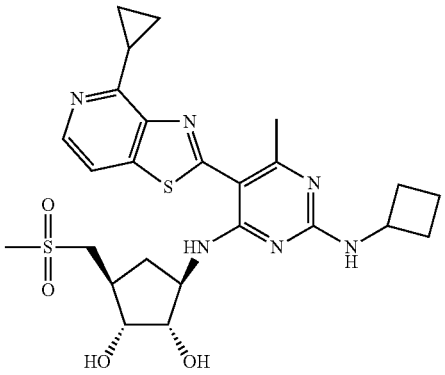
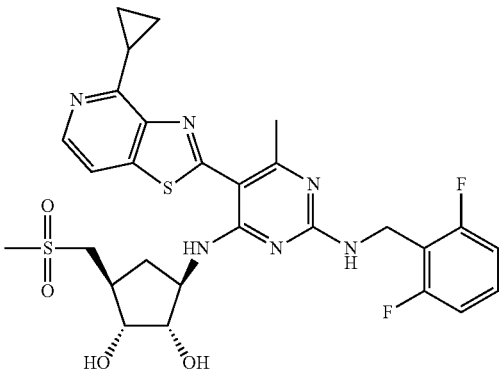
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
3239		0.010	535.2
3438		0.011	561.2
3513		0.054	545.3
3538		0.007	617.4

TABLE IV-continued

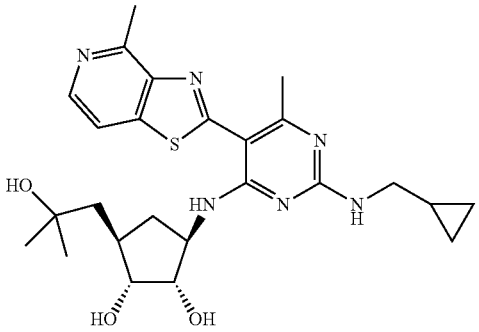
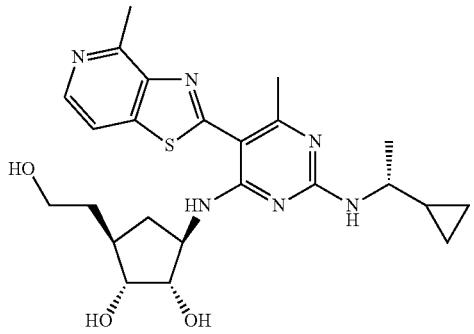
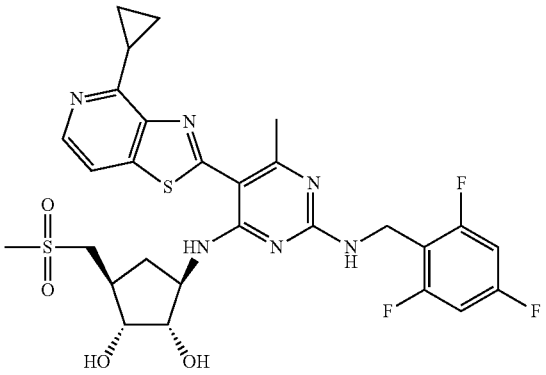
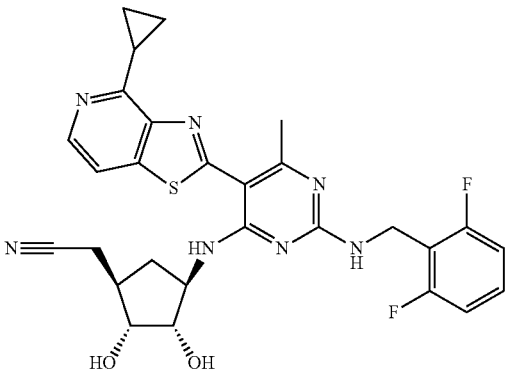
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
3552		0.024	499.4
3561		0.023	485.4
3563		0.003	635.3
3569		0.016	564.3

TABLE IV-continued

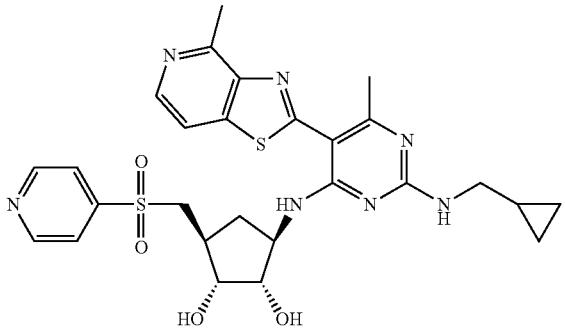
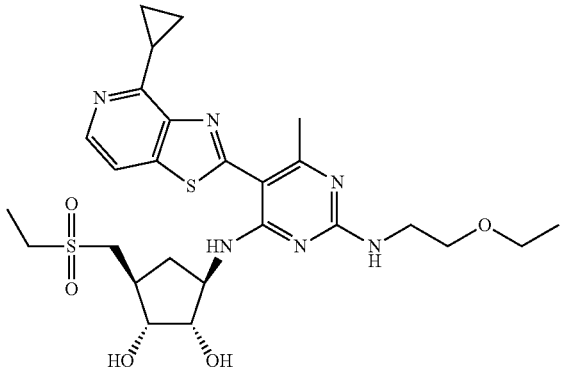
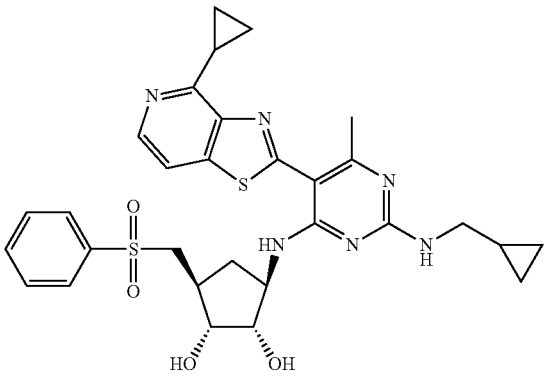
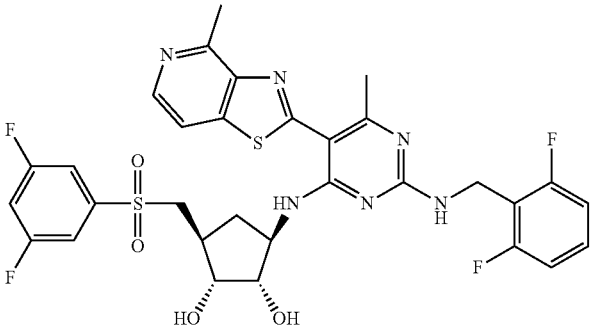
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
3580		0.012	582.1
3721		0.024	577.2
3744		0.044	607.2
3754		0.015	689.30

TABLE IV-continued

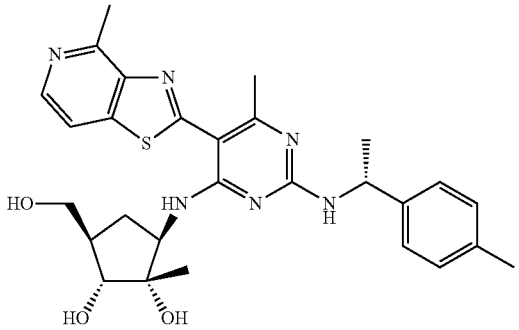
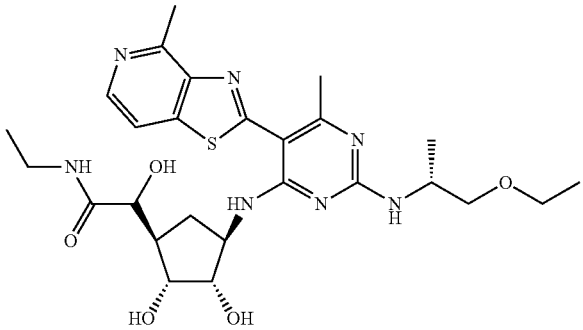
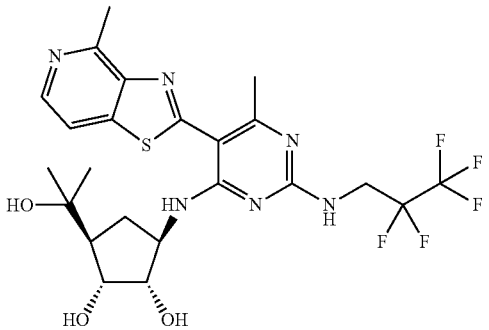
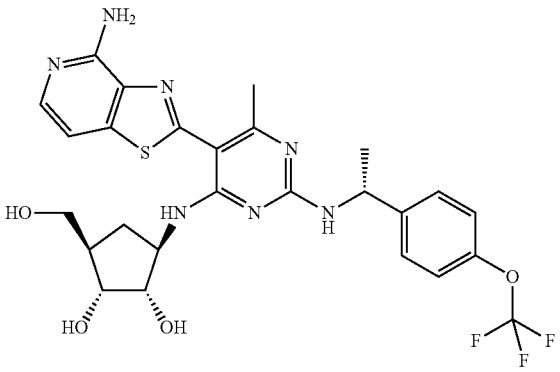
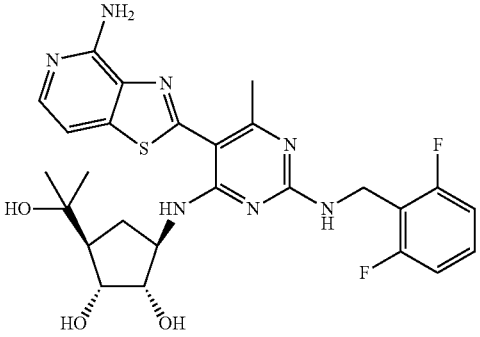
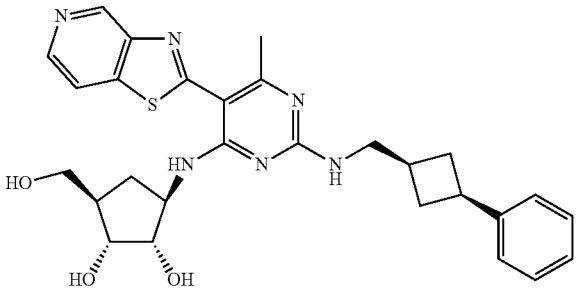
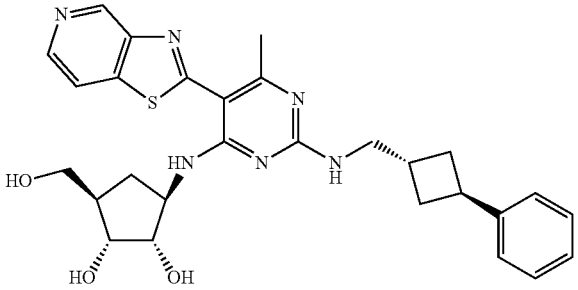
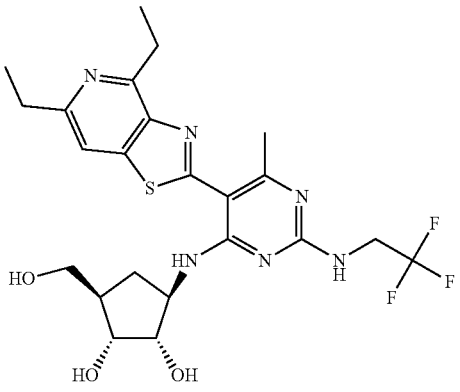
Cmpd #	Structure	EC90 (uM)	MS (M + H)+
3815		0.030	535.30
4025		0.008	560
4346		0.043	563.2
4413		0.121	592.3

TABLE IV-continued

Cmpd #	Structure	EC90 (uM)	MS (M + H)+
4443		0.055	558.3
4512		0.019	533.3
4513		0.016	533.3
4706		0.045	527.2

Tables V and VI display representative compounds that were synthesized and characterized. The tables display the range of HCV Replicon assay values obtained using the above method. EC90 ranges are identified as follows:

Code	EC90 Range (μM)
A	≤0.5
B	>0.5, ≤5.0
C	>5, ≤25
D	>25

TABLE V

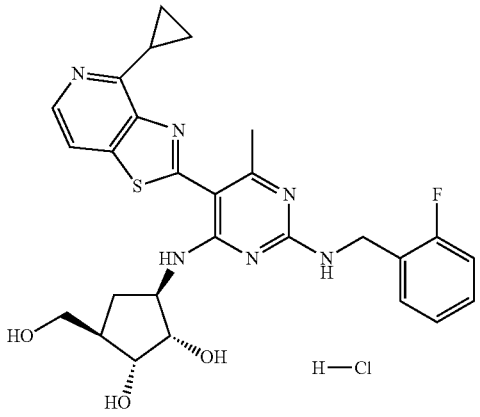
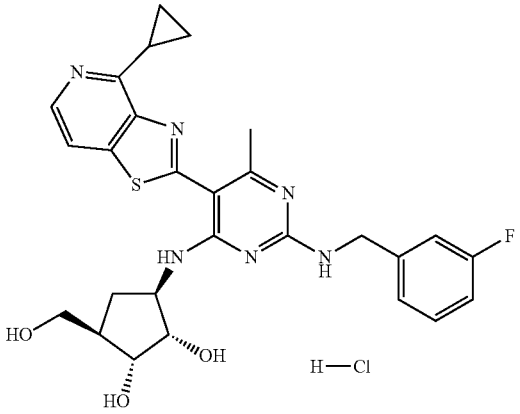
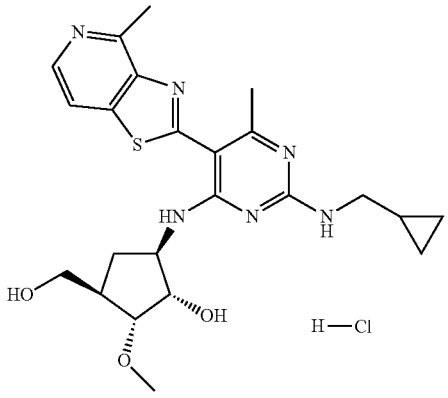
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4901		A	DMSO-d6) δ 0.98-1.18 (m, 1H), 1.14-1.22 (m, 2H), 1.23 (br s, 2H), 1.86-2.04 (m, 2H), 2.43 (s, 3H), 2.94-3.04 (m, 1H), 3.63-3.68 (m, 1H), 3.70-3.76 (m, 1H), 3.97-4.05 (m, 1H), 4.39 (app quint, 1H, J = 7.9 Hz), 4.67 (dd, 1H, J = 5.9, 15.3 Hz), 4.76 (dd, 1H, J = 5.9, 15.3 Hz), 7.18-7.26 (m, 2H), 7.32-7.40 (m, 1H), 7.50 (t, 1H, J = 7.5 Hz), 8.05 (d, 1H, J = 5.5 Hz), 8.36 (br s, 1H), 8.41 (d, 1H, J = 5.4 Hz), 9.11 (br s, 1H).	537.2
4902		A	(DMSO-d6) δ 1.01-1.10 (m, 1H), 1.20-1.28 (m, 2H), 1.33 (br s, 2H), 1.85-2.07 (m, 2H), 2.44 (s, 3H), 2.96-3.04 (m, 1H), 3.31 (app d, 2H, J = 5.0 Hz), 3.63-3.68 (m, 1H), 3.72 (dd, 1H, J = 5.4, 7.2 Hz), 4.38 (app quint, 1H, J = 7.7 Hz), 4.62-4.74 (m, 2H), 7.11 (dt, 1H, J = 2.2, 9.0 Hz), 7.23 (br s, 1H), 7.27 (d, 1H, J = 7.6 Hz), 7.38-7.45 (m, 1H), 8.15 (br d, 1H, J = 4.9 Hz), 8.44 (d, 1H, J = 5.7 Hz), 8.50 (br s, 1H), 9.02 (br s, 1H).	537.2
4903		A	(DMSO-d6) δ 0.21-0.27 (m, 2H), 0.40-0.46 (m, 2H), 1.03-1.20 (m, 2H), 2.07 (br s, 1H), 2.34-2.48 (m, 1H), 2.60 (s, 3H), 2.87 (s, 3H), 23.12-3.32 (2H), 3.33-3.41 (m, 2H), 3.39-3.46 (m, 1H), 3.95 (br s, 1H), 4.25 (br s, 1H), 4.61 (br s, 1H), 4.64-4.71 (m, 1H), 7.42 (br s, 1H), 7.96 (d, 1H, J = 5.5 Hz), 8.31 (d, 1H, J = 5.3 Hz), 9.96 (br s, 1H).	471.2

TABLE V-continued

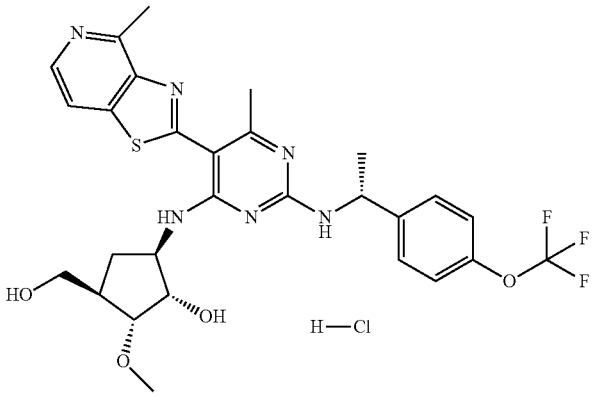
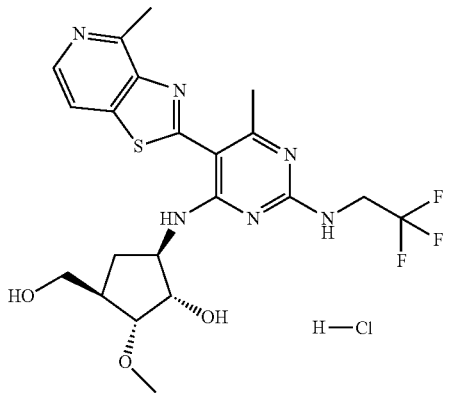
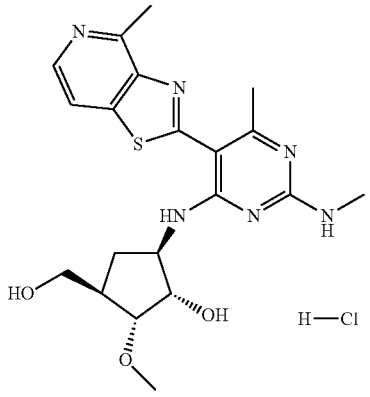
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4904		A	(DMSO-d6) δ 0.74-0.84 (m, 1H), 1.45 (d, 3H, J = 7.0 Hz), 1.76-1.86 (m, 1H), 1.94-2.08 (m, 1H), 2.58 (s, 3H), 2.84 (s, 3H), 3.20-3.32 (m, 2H), 3.34 (s, 3H), 3.40 (app t, 1H, J = 4.7 Hz), 3.86 (app q, 1H, J = 6.7 Hz), 4.13-4.23 (m, 1H), 4.53-4.58 (m, 1H), 4.66 (d, 1H, J = 6.6 Hz), 5.04-5.14 (m, 1H), 7.29 (d, 1H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.4 Hz), 7.95 (d, 1H, J = 5.3 Hz), 7.98 (d, 1H, J = 7.3 Hz), 8.31 (d, 1H, J = 5.5 Hz), 9.66 and 9.73 (br s and d, 1H, J = 6.0 Hz).	605.2
4905		A	(DMSO-d6) δ 1.13 (br s, 1H), 2.08 (br s, 1H), 2.32-2.45 (m, 1H), 2.60 (s, 3H), 2.89 (s, 3H), 3.31 (s, 3H), 3.34-3.40 (m, 2H), 3.40-3.44 (m, 1H), 3.95 (br s, 1H), 4.12 (br s, 1H), 4.23 (br s, 1H), 4.57-4.63 (m, 1H), 4.65 (d, 1H, J = 6.5 Hz), 7.86 (br s, 1H), 7.99 (d, 1H, J = 5.3 Hz), 8.35 (d, 1H, J = 5.5 Hz), 9.75 (br s, 1H).	499.2
4906		B	—	431.2

TABLE V-continued

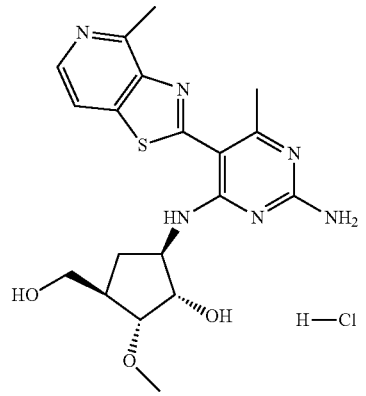
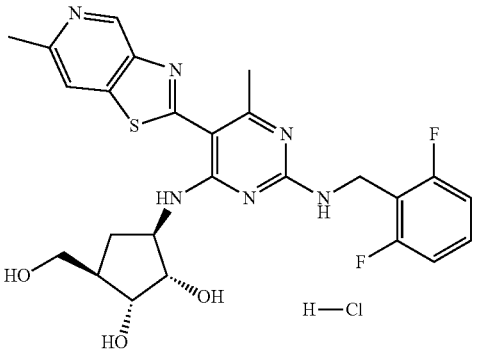
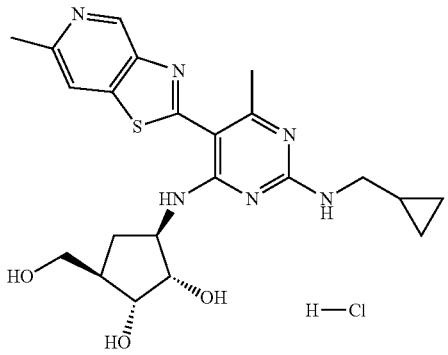
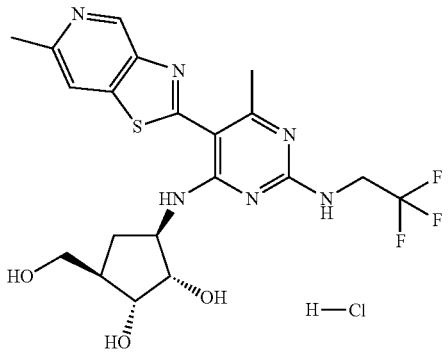
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4907		A	(DMSO-d6) δ 1.06 (dt, 1H, J = 8.2, 13.1 Hz), 2.00-2.09 (m, 1H), 2.32-2.41 (m, 1H), 2.57 (s, 3H), 2.87 (s, 3H), 3.36 (app q, 1H, J = 5.3 Hz), 3.41 (t, 1H, J = 4.5 Hz), 3.83-3.89 (m, 1H), 4.31 (app quint, 1H, J = 7.4 Hz), 4.62 (t, 1H, J = 5.1 Hz), 4.68 (d, 1H, J = 6.2 Hz), 6.72 (s, 2H, 7.96 (d, 1H, J = 5.3 Hz), 8.32 (d, 1H, J = 5.4 Hz), 9.75 (d, 1H, J = 6.5 Hz).	417.2
4908		A	(DMSO-d6) δ 1.09 (dt, 1H, J = 8.4, 12.9 Hz), 1.90-2.03 (m, 1H), 2.04-2.17 (m, 1H), 2.33 (br s, 1H), 2.40 (br s, 3H), 2.69 (s, 3H), 3.32-3.43 (m, 2H), 3.69 (app t, 1H, J = 5.1 Hz), 3.80 (app t, 1H, J = 6.3 Hz), 4.37-4.62 (m, 2H), 4.64-4.74 (m, 1H), 4.76-4.86 (m, 1H), 7.13 (app t, 2H, J = 8.0 Hz), 7.38-7.48 (m, 1H), 8.27 (br s, 1H), 8.36 (br s, 1H), 9.00 (br s, 1H), 9.39 (s, 1H).	529.2
4909		A	(DMSO-d6) δ 0.30-0.35 (m, 2H), 0.48-0.54 (m, 2H), 1.10-1.25 (m, 2H), 1.90-2.00 (m, 1H), 2.15-2.26 (m, 1H), 2.43 (s, 3H), 2.71 (s, 3H), 3.29-3.42 (m, 4H), 3.69 (t, 1H, J = 4.9 Hz), 3.76-3.84 (m, 1H), 4.35-4.44 (m, 1H), 7.99 (br s, 1H), 8.31 (s, 1H), 8.98 (br s, 1H), 9.43 (s, 1H).	457.2
4910		A	(DMSO-d6) δ 1.16-1.26 (m, 1H), 1.90-2.00 (m, 1H), 2.18-2.28 (m, 1H), 2.75 (s, 3H), 3.34-3.43 (m, 2H), 3.70 (t, 1H, J = 5.1 Hz), 3.80 (t, 1H, J = 5.7 Hz), 4.22-4.44 (3H), 8.34 (br s, 1H), 8.41 (br s, 1H), 9.10 (br s, 1H), 9.49 (1H).	485.2

TABLE V-continued

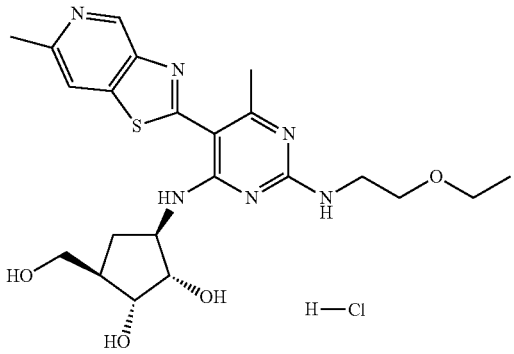
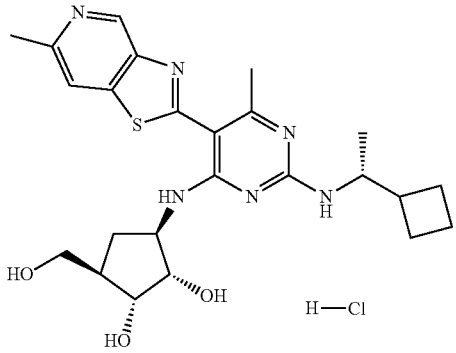
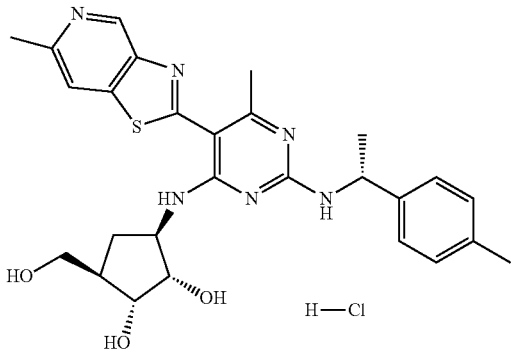
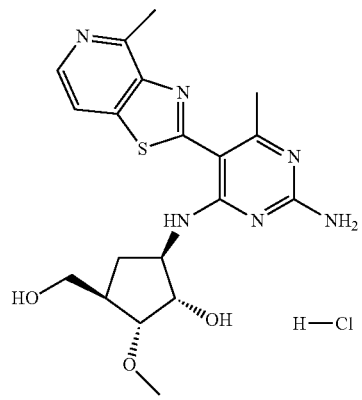
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4911		A	(DMSO-d6) δ 1.14 (t, 3H, J = 7.1 Hz), 1.16-1.25 (m, 1H), 1.88-1.98 (m, 1H), 2.17-2.26 (m, 1H), 2.44 (s, 3H), 2.74 (s, 3H), 3.32-3.41 (m, 2H), 3.50 (q, 2H, J = 7.1 Hz), 3.56-3.66 (m, 3H), 3.69 (t, 1H, J = 5.0 Hz), 3.80 (t, 1H, J = 5.7 Hz), 4.34-4.44 (app quint, 1H, J = 7.5 Hz), 7.91 (br s, 1H), 8.38 (br s, 1H), 9.00 (br s, 1H), 9.49 (br s, 1H).	475.2
4912		A	(DMSO-d6) δ 1.14 (d, 3H, J = 6.3 Hz), 1.16-1.26 (m, 1H), 1.72-1.90 (m, 3H), 1.90-2.20 (m, 3H), 2.17-2.28 (m, 1H), 2.44 (s, 3H), 2.73 (s, 3H), 3.32-3.43 (m, 2H), 3.70 (app t, 1H, J = 4.8 Hz), 3.67-3.86 (m, 1H), 4.08-4.18 (m, 1H), 4.33-4.43 (m, 1H), 8.00 (br d, 1H, J = 7.8 Hz), 8.36 (br s, 1H), 9.04 (br d, 1H, J = 6.2 Hz), 9.49 (br s, 1H).	485.2
4913		A	(DMSO-d6) δ 0.60-1.15 (m, 1H), 1.52 (d, 3H, J = 6.8 Hz), 1.72-1.83 (m, 1H), 1.86-1.96 (m, 1H), 2.28 (s, 3H), 2.40 (s, 3H), 2.71 (s, 3H), 3.28-3.42 (m, 2H), 3.68 (app t, 1H, J = 5.0 Hz), 3.76 (app t, 1H, J = 6.1 Hz), 4.37 (app quint, 1H, J = 7.6 Hz), 5.06-5.16 (m, 1H), 7.17 (d, 1H, J = 7.8 Hz), 7.33 (d, 1H, J = 8.0 Hz), 8.32 (br s, 1H), 8.54 (br d, 1H, J = 6.5 Hz), 8.92 (br d, 1H, J = 5.7 Hz), 9.43 (br s, 1H).	521.2
4914		A	(DMSO-d6) δ 1.12 (dt, 1H, J = 8.4, 13.1 Hz), 1.85-1.95 (m, 1H), 2.15 (dt, 1H, J = 8.8, 13.1 Hz), 3.30-3.40 (m, 2H), 4.47 (quint, 1H, J = 8.0 Hz), 8.35 (br s, 1H), 8.75 (d, 1H, J = 7.6 Hz), 9.47 (br s, 1H).	403.2

TABLE V-continued

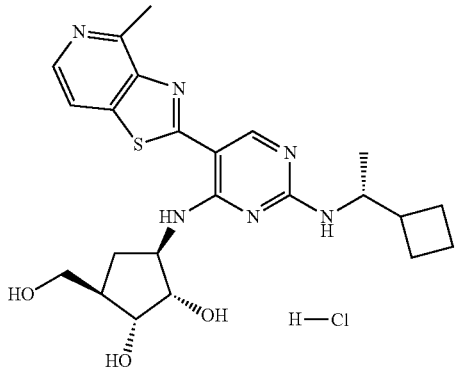
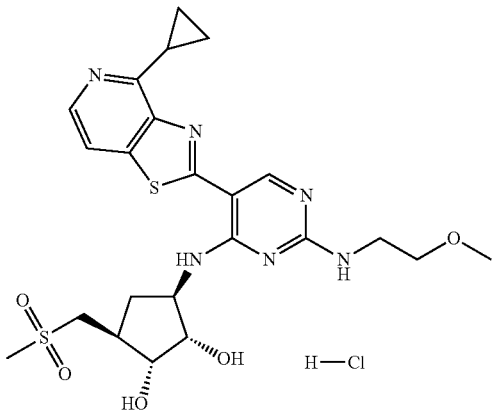
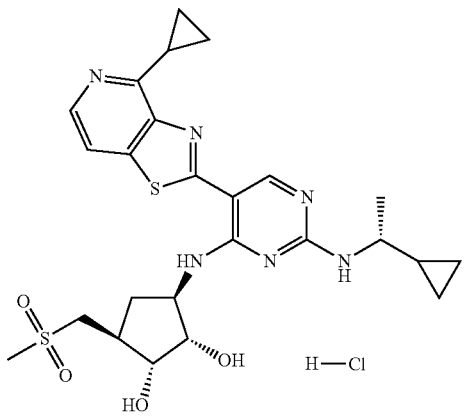
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4915		>1.0	(DMSO-d6) δ 1.04 (m, 1H), 1.13 (d, 3H, J = 6.7 Hz), 1.22-1.32 (m, 1H), 1.70-1.89 (m, 4H), 1.90-2.04 (m, 2H), 2.00-2.10 (m, 1H), 2.40-2.50 (m, 1H), 3.02 (s, 3H), 3.43 (d, 3H, J = 5.3 Hz), 3.60-3.84 (m, 2H, 3.88-3.95 (m, 1H), 4.08-4.20 (m, 1H), 4.35 (app quint, 1H, J = 7.4 Hz), 8.37-8.50 (m, 2H), 8.57 (br d, 1H, J = 6.1 Hz), 8.80 (s, 1H), 9.98 (br s, 1H).	470.2
4916		B	(DMSO-d6) δ 1.27-1.46 (m, 3H), 2.34-2.47 (m, 1H), 2.65-2.74 (m, 1H), 2.87-2.95 (m, 1H), 3.00 (s, 3H), 3.11 (dd, 1H, J = 9.9, 13.9 Hz), 3.31 (s, 3H), 3.45 (dd, J = 4.3, 13.9 Hz), 3.54-3.59 (m, 1H), 3.61-3.69 (m, 1H), 3.72-3.77 (m, 1H), 3.95 (app t, 1H, J = 5.2 Hz), 4.27-4.36 (m, 1H), 8.17 (br d, 1H, J = 5.1 Hz), 8.43 (d, 1H, J = 5.9 Hz), 8.46-8.55 (m, 1H), 8.80 (s, 1H), 10.13 (br s, 1H).	535.2
4917		>0.2	(DMSO-d6) δ 0.27-0.56 (m, 4H), 1.02-1.12 (m, 1H), 1.22-1.44 (m, 3H), 1.30 (d, 3H, J = 6.7 Hz), 2.34-2.46 (m, 1H), 2.63-2.72 (m, 1H), 2.85-2.93 (m, 2H), 3.00 (s, 3H), 3.05-3.14 (m, 1H), 3.44 (dd, 1H, J = 4.1, 13.9 Hz), 3.63-3.73 (m, 1H), 3.73 (dd, 1H, J = 5.3, 6.7 Hz), 3.90-3.95 (m, 1H), 4.20-4.29 (m, 1H), 8.09-8.19 (m, 1H), 8.41 (d, 1H, J = 5.7 Hz), 8.64 (br d, 1H, J = 6.9 Hz), 8.78 (s, 1H), 10.12 (br s, 1H).	545.2

TABLE V-continued

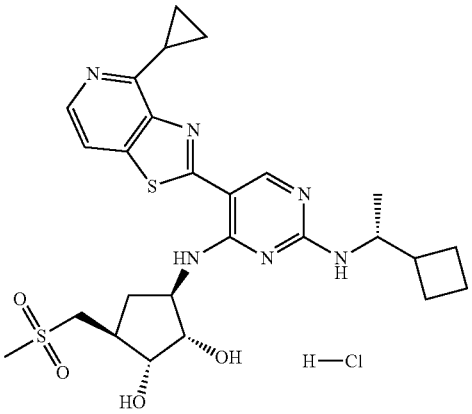
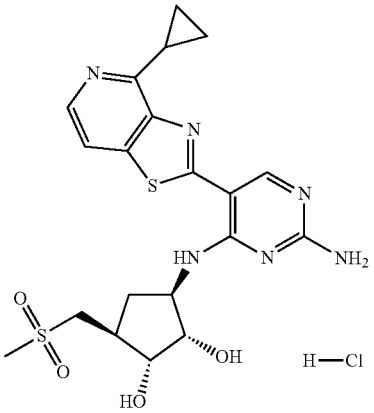
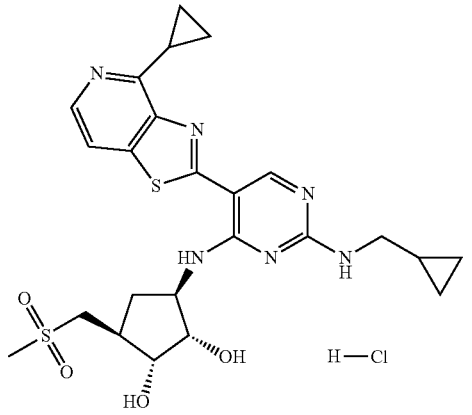
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4918		A	(DMSO-d6) δ 1.07-1.17 (m, 2H), 1.22-1.46 (m, 4H), 1.72-1.90 (m, 2H), 1.90-2.04 (m, 2H), 2.37-2.52 (m, 2H), 2.67-2.77 (m, 1H), 2.86-2.94 (m, 1H), 2.99 (s, 3H), 3.11 (dd, 1H, J = 10.1, 13.8 Hz), 3.45 (app dd, 1H, J = 4.0, 14.0 Hz), 3.73 (t, 1H, J = 6.4 Hz), 3.96 (t, 1H, J = 5.2 Hz), 4.12-4.21 (m, 1H), 4.26-4.38 (m, 1H), 8.10-8.21 (m, 1H), 8.42 (d, 1H, J = 5.7 Hz), 8.57 (br d, 1H, J = 7.6 Hz), 8.80 (s, 1H), 10.14 (br s, 1H).	559.2
4919		A	(DMSO-d6) δ 1.22-1.42 (m, 5H), 2.30-2.41 (m, 1H), 2.60-2.71 (m, 1H), 2.87-2.94 (m, 1H), 3.00 (s, 3H), 3.14 (app dd, 1H, J = 9.6, 13.5 Hz), 3.45 (app dd, 1H, J = 4.2, 14.0 Hz), 3.76 (t, 1H, J = 5.7 Hz), 3.94 (t, 1H, J = 5.9 Hz), 4.29-4.38 (m, 1H), 8.10 (d, 1H, J = 5.4 Hz), 8.42 (d, 1H, J = 5.7 Hz), 8.54-8.83 (br s, 1H), 8.77 (s, 1H), 10.21 (br d, 1H, J = 5.5 Hz).	477.1
4920		A	(DMSO-d6) δ 0.28-0.35 (m, 2H), 0.48-0.54 (m, 2H), 1.09-1.20 (m, 1H), 1.22-1.45 (m, 3H), 2.34-2.48 (m, 1H), 2.65-2.75 (m, 1H), 2.86-2.94 (m, 2H), 3.00 (s, 3H), 3.04-3.15 (m, 1H), 3.27-3.44 (m, 2H), 3.44 (dd, 1H, J = 4.4, 13.9 Hz), 3.72-3.78 (m, 1H), 3.91-3.97 (m, 1H), 4.25-4.35 (m, 1H), 8.12 (br d, 1H, J = 4.9 Hz), 8.42 (d, 1H, J = 5.7 Hz), 8.54-8.62 (m, 1H), 8.77 (s, 1H), 10.16 (br s, 1H).	531.2

TABLE V-continued

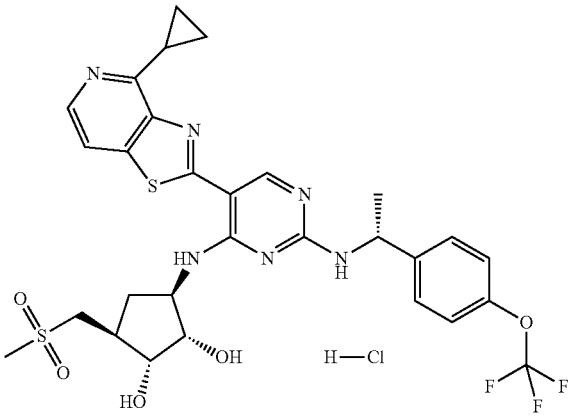
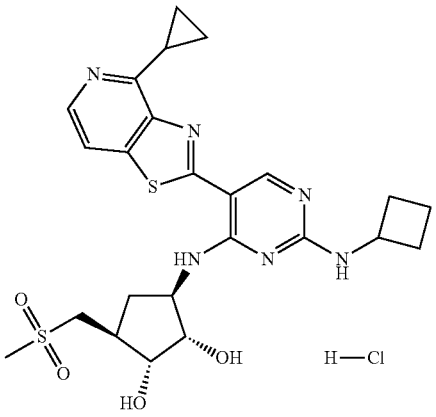
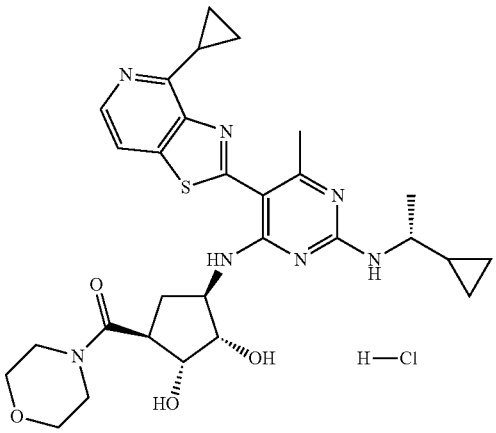
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4921		B	(DMSO-d6) δ 1.18-1.42 (m, 4H), 1.43-1.56 (m, 1H), 1.54 (d, 3H, J = 6.8 Hz), 2.31-2.48 (m, 2H), 2.82-2.91 (m, 1H), 2.97-3.16 (m, 1H), 3.00 (s, 3H), 3.45 (dd, 1H, J = 4.0, 13.9 Hz), 3.74 (app t, 1H, J = 5.6 Hz), 3.92 (app t, 1H, J = 5.1 Hz), 4.27-4.40 (m, 1H), 5.29 (app quint, 1H, J = 7.0 Hz), 7.37 (d, 2H, J = 8.2 Hz), 7.56-7.66 (m, 2H), 8.10-8.20 (m, 1H), 8.40 (d, 1H, J = 5.7 Hz), 8.72 (s, 1H), 9.09-9.18 (m, 1H), 9.87 (br s, 1H).	665.2
4922		>0.3	(DMSO-d6) δ 1.24-1.45 (m, 5H), 1.70-1.82 (m, 2H), 2.00-2.15 (m, 2H), 2.30-2.48 (m, 3H), 2.65-2.79 (m, 1H), 2.82-2.95 (m, 1H), 3.00 (s, 3H), 3.07-3.16 (m, 1H), 3.45 (dd, 1H, J = 4.2, 14.0 Hz), 3.75 (app t, 1H, J = 6.4 Hz), 3.90-3.97 (m, 1H), 4.25-4.35 (m, 1H), 4.38-4.52 (m, 1H), 8.08-8.18 (m, 1H), 8.41 (d, 1H, J = 5.7 Hz), 8.73 (s, 1H), 8.83 (br s, 1H), 10.09 (br s, 1H).	531.2
4923		A	(DMSO-d6) δ 0.28-0.57 (m, 4H), 1.02-1.12 (m, 1H), 1.28-1.37 (m, 5H), 1.47 (br s, 2H) 1.56-1.65 (m, 1H), 2.26-2.37 (m, 1H), 2.44 (s, 3H), 3.02-3.14 (m, 2H), 3.14-3.63 (m, 8H), 3.63-3.73 (m, 1H), 3.82 (app t, 1H, J = 4.9 Hz), 3.90 (app t, 1H, J = 4.7 Hz), 4.32-4.43 (m, 1H), 8.24 (br d, 1H, J = 7.6 Hz), 8.28 (br d, 1H, J = 5.0 Hz), 8.46 (d, 1H, J = 5.9 Hz), 9.08 (br s, 1H).	580.3

TABLE V-continued

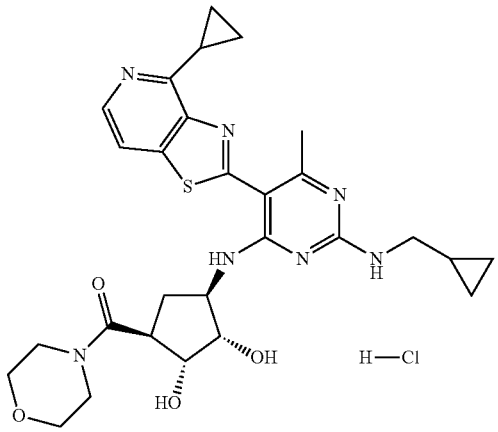
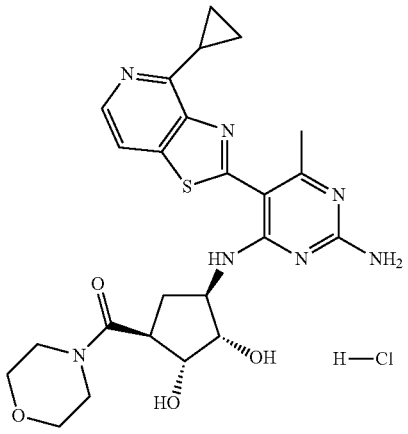
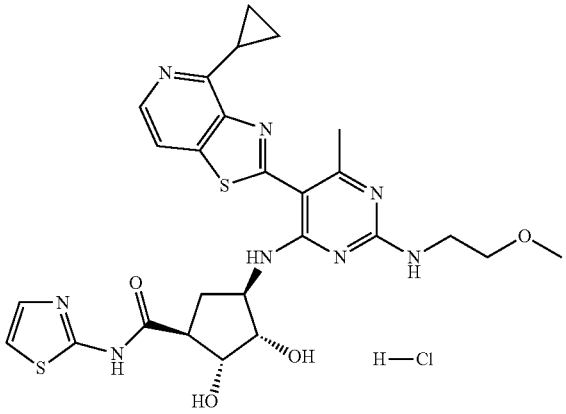
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4924		A	(DMSO-d6) δ 0.30-0.35 (m, 2H), 0.40-0.54 (m 2H), 1.10-1.20 (m, 1H), 1.24-1.31 (m, 2H), 1.38 (br s, 2H), 1.61 (app quint, 1H, J = 6.6 Hz), 2.28-2.38 (m, 1H), 3.05-3.14 (m, 2H), 3.14-3.35 (m, 1H), 3.37 (app t, 2H, J = 6.3 Hz), 3.39-3.62 (m, 8H), 3.81 (app t, 1H, J = 5.1 Hz), 3.90 (app t, 1H, J = 4.7 Hz), 4.45 (app quint, 1H, J = 4.7 Hz), 8.13 (br s, 1H), 8.2) (br d, 1H, J = 5.2 Hz), 8.45 (d, 1H, J = 8.9 Hz), 9.14 (br s, 1H).	566.3
4925		A	(DMSO-d6) δ 1.36-1.46 (m, 2H), 1.53-1.63 (m, 3H), 2.24-2.36 (m, 3H), 2.40 (s, 3H), 3.00-3.14 (m, 2H), 3.14-3.35 (m, 2H), 3.40-3.62 (m, 6H), 3.78 (app t, 2H, J = 6.0 Hz), 3.88 (app t, 1H, J = 4.4 Hz), 4.51 (app quint, 1H, J = 7.2 Hz), 8.39 (br d, 1H, J = 5.9 Hz), 8.49 (d, 1H, J = 6.0 Hz), 8.81 (d, 1H, J = 7.3 Hz), 13.58 (br s, 1H).	512.2
4926		A	(DMSO-d6) δ 1.48 (br dd, 2H, J = 2.4, 8.4 Hz), 1.56-1.68 (m, 1H), 1.67-1.78 (m, 2H), 2.43-2.52 (m, 1H), 2.47 (s, 3H), 2.69 (s, 3H), 3.06-3.16 (m, 2H), 3.32 (s, 3H), 3.57 (app t, 1H, J = 5.4 Hz), 3.64-3.72 (m, 1H), 3.93 (app t, 1H, J = 4.6 Hz), 4.05 (app t, 1H, J = 5.4 Hz), 4.41-4.50 (m, 1H), 7.20 (d, 1H, J = 3.7 Hz), 7.46 (d, 1H, J = 3.5 Hz), 8.14-8.21 (m, 1H), 8.50-8.56 (m, 1H), 8.53 (s, 1H), 12.23 (br s, 1H).	583.2

TABLE V-continued

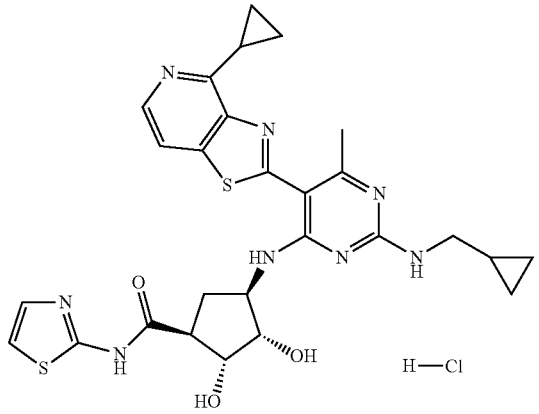
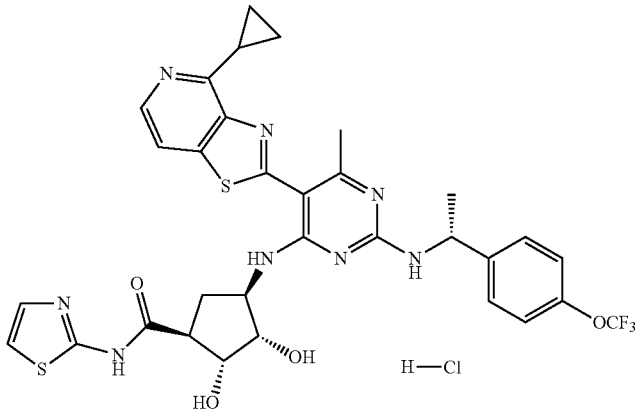
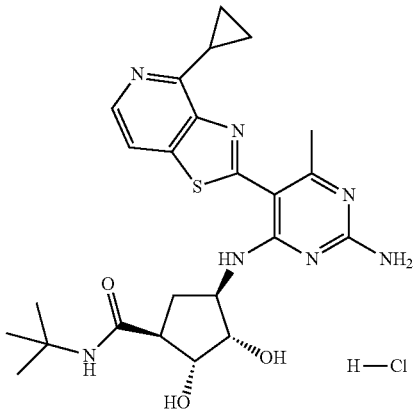
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4927		A	(DMSO-d6) δ 0.30-0.37 (m, 2H), 0.48-0.56 (m, 2H), 1.10-1.22 (m, 1H), 1.37 (br d, 2H, J = 7.6 Hz), 1.48 (br s, 2H), 1.56-1.67 (m, 1H), 2.48 (s, 3H), 2.69 (s, 3H), 3.04-3.14 (m, 2H), 3.40 (t, 2H, J = 6.2 Hz), 3.91 (app t, 1H, J = 4.5 Hz), 4.05 (app t, 1H, J = 5.3 Hz), 4.41-4.50 (m, 1H), 7.19 (d, 1H, J = 3.4 Hz), 7.46 (d, 1H, J = 3.6 Hz), 8.18-8.26 (m, 1H), 8.26-8.38 (m, 1H), 8.49 (app d, 1H, J = 5.6 Hz), 9.13 (br s, 1H), 12.20 (br s, 1H).	579.2
4928		A	(DMSO-d6) δ 1.07-1.28 (m, 4H), 1.30-1.42 (m, 1H), 1.46 (d, 3H, J = 6.9 Hz), 2.18-2.29 (m, 1H), 2.58 (s, 3H), 2.96-3.04 (m, 1H), 3.06-3.15 (m, 1H), 3.82-3.92 (m, 1H), 4.04-4.11 (m, 1H), 4.22-4.30 (m, 1H), 4.99-5.05 (m, 2H), 5.14-5.23 (m, 1H), 7.21 (d, 1H, J = 3.6 Hz), 7.28 (app d, 1H, J = 8.2 Hz), 7.48 (d, 1H, J = 3.5 Hz), 7.57 (app d, 1H, J = 8.6 Hz), 7.85 (d, 1H, J = 5.3 Hz), 8.05 (br d, 1H, J = 7.7 Hz), 8.28 (d, 1H, J = 5.5 Hz), 9.83 (d, 1H, J = 6.4 Hz), 12.12 (s, 1H).	713.2
4929		A	(DMSO-d6) δ 1.02 (s, 9H), 1.27-1.34 (m, 2H), 1.34-1.42 (m, 1H), 1.39-1.46 (m, 2H), 2.23-2.32 (m, 1H), 2.36 (s, 3H), 2.56-2.63 (m, 1H), 3.02-3.10 (m, 1H), 3.78 (t, 2H, J = 4.7 Hz), 3.82 (t, 1H, J = 4.5 Hz), 4.39-4.48 (m, 1H), 7.60 (br s, 1H), 8.24 (br s, 1H), 8.46 (d, 1H, J = 5.8 Hz), 9.07 (br d, 1H, J = 6.3 Hz), 13.21 (br s, 1H).	498.2

TABLE V-continued

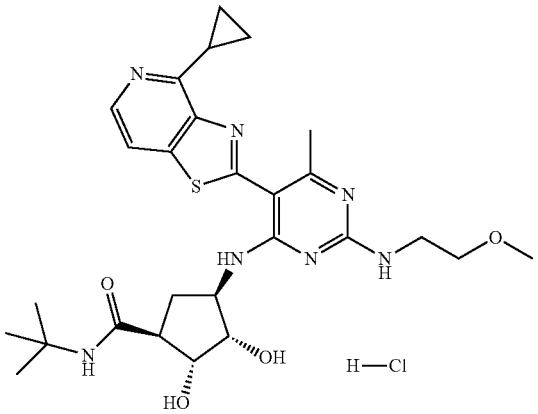
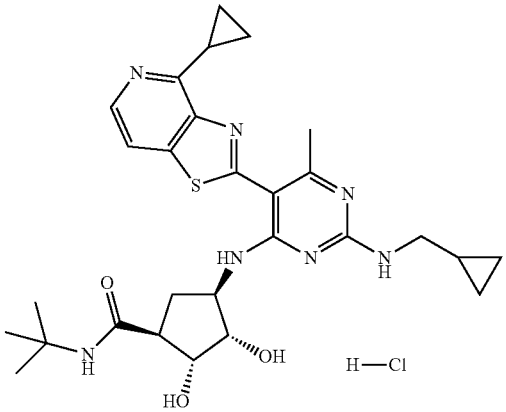
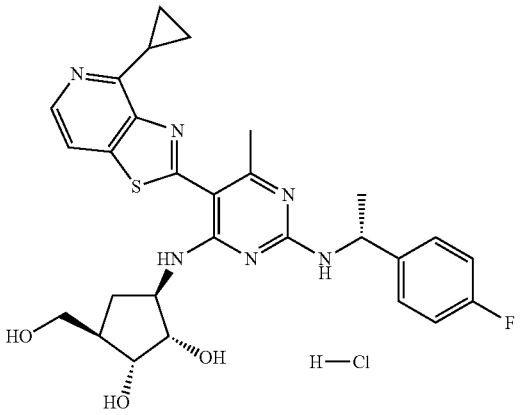
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4930		A	(DMSO-d6) δ 1.01 (s, 9H), 1.32-1.46 (m, 3H), 1.51 (br s, 2H), 2.27-2.37 (m, 1H), 2.40 (s, 3H), 2.59-2.66 (m, 1H), 3.03-3.11 (m, 1H), 3.32 (s, 3H), 3.53-3.58 (m, 2H), 3.62-3.69 (m, 2H), 3.79-3.84 (m, 2H), 4.34-4.42 (m, 1H), 7.60-7.64 (m, 1H), 8.03 (br s, 1H), 8.28-8.34 (m, 1H), 8.47 (d, 1H, J = 5.9 Hz), 9.23 (br s, 1H).	556.3
4931		A	(DMSO-d6) δ 0.31-0.36 (m, 2H), 0.48-0.54 (m, 2H), 1.01 (s, 9H), 1.10-1.22 (m, 1H), 1.31-1.39 (m, 2H), 1.37-1.45 (m, 1H), 1.51 (br s, 2H), 2.27-2.37 (m, 1H), 2.40 (s, 3H), 2.59-2.67 (m, 1H), 3.03-3.11 (m, 1H), 3.37 (app t, 2H, J = 6.3 Hz), 3.79-3.84 (m, 2H), 4.34-4.42 (m, 1H), 7.59-7.65 (m, 1H), 8.14-8.21 (m, 1H), 8.28-8.34 (m, 1H), 8.47 (d, 1H, J = 6.1 Hz), 9.21 (br s, 1H), 13.53 (br s, 1H).	552.3
4932		A	(DMSO-d6) δ 0.88-1.00 (m, 1H), 1.23-1.33 (m, 2H), 1.40 (br s, 2H), 1.54 (d, 3H, J = 6.9 Hz), 1.66-1.78 (m, 1H), 1.86-1.96 (m, 1H), 2.42 (s, 3H), 2.95-3.03 (m, 1H), 3.26-3.35 (m, 2H), 3.64-3.69 (m, 1H), 3.69-3.75 (m 1H), 4.36 (quint, 1H, J = 7.8 Hz), 5.10-5.20 (m, 1H), 7.19 (t, 1H, J = 8.9 Hz), 7.49 (dd, 1H, J = 5.6, 8.3 Hz), 8.21 (br dd, 1H, J = 5.1 Hz), 8.45 (d, 1H, J = 5.6 Hz), 8.74 (br d, 1H, J = 6.9 Hz), 8.94 (br s, 1H).	551.2

TABLE V-continued

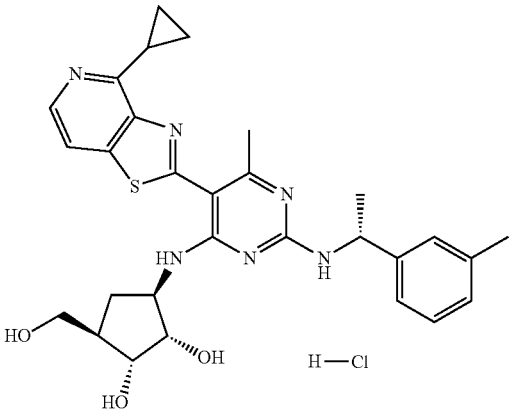
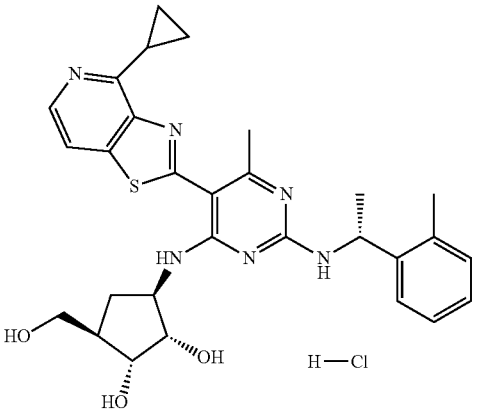
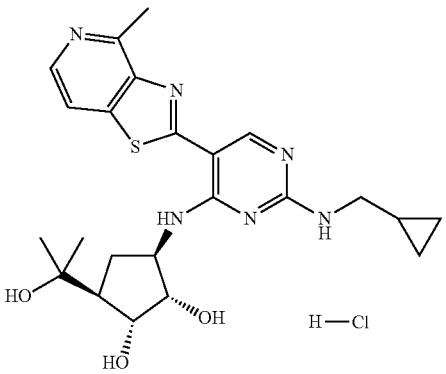
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4933		A	(DMSO-d6) δ 0.90-1.00 (m, 1H), 1.25-1.33 (m, 2H), 1.41 (br s, 2H), 1.53 (d, 3H, J = 6.9 Hz), 1.75-1.84 (m, 1H), 1.87-1.97 (m, 1H), 2.32 (s, 3H), 2.42 (s, 3H), 2.95-3.30 (m, 1H), 3.26-3.35 (m, 2H), 3.65-3.70 (m, 1H), 3.70-3.76 (m 1H), 4.18 (app quint, 1H, J = 7.8 Hz), 5.06-5.16 (m, 1H), 7.06-7.11 (m, 1H), 7.21-7.28 (m, 3H), 8.22 (br dd, 1H, J = 4.7 Hz), 8.45 (d, 1H, J = 5.9 Hz), 8.73 (br d, 1H, J = 6.8 Hz), 8.93 (br s, 1H).	547.2
4934		A	(DMSO-d6) δ 0.72-0.88 (m, 1H), 1.22-1.32 (m, 2H), 1.38 (br s, 2H), 1.49 (d, 3H, J = 6.8 Hz), 1.48-1.58 (m, 1H), 1.78-1.98 (m, 1H), 2.43 (s, 6H), 2.94-3.20 (m, 1H), 3.20-3.33 (m, 2H), 3.63-3.72 (m, 2H), 4.25-4.39 (m, 1H), 5.27-5.38 (m, 1H), 7.12-7.24 (m, 3H), 7.37 (d, 1H, J = 7.4 Hz), 8.20 (br dd, 1H, J = 4.9 Hz), 8.44 (d, 1H, J = 4.9 Hz), 8.82 (d, 1H, J = 6.7 Hz), 8.99 (br s, 1H), 13.32 (br s., 1H)..	547.2
4935		A	(DMSO-d6) δ 0.26-0.35 (m, 2H), 0.44-0.56 (m 2H), 1.07 (s, 3H), 1.15-1.23 (m, 1H), 1.18 (s, 3H), 1.36-1.48 (m, 1H), 1.82-1.90 (m, 1H), 2.29-2.39 (m, 1H), 2.50 (s, 3H), 3.26-3.44 (m, 2H), 3.74-3.80 (m, 1H), 3.90-3.95 (m, 1H), 4.30 (app quint, 1H, J = 7.2 Hz), 8.54 (d, 1H, J = 6.1 Hz), 8.60 (d, 1H, J = 6.1 Hz), 8.65-8.73 (m, 1H, 8.86 (s, 1H), 10.03 (br d, 1H, J = 4.9 Hz).	471.2

TABLE V-continued

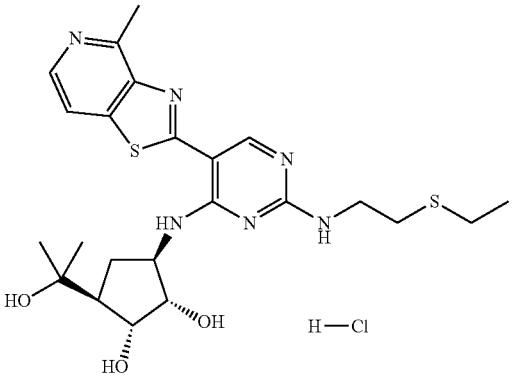
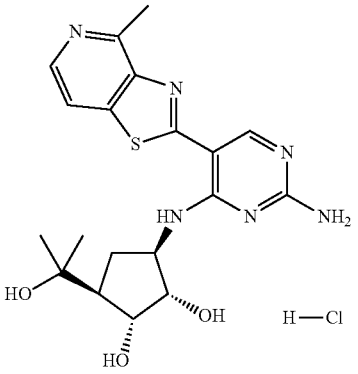
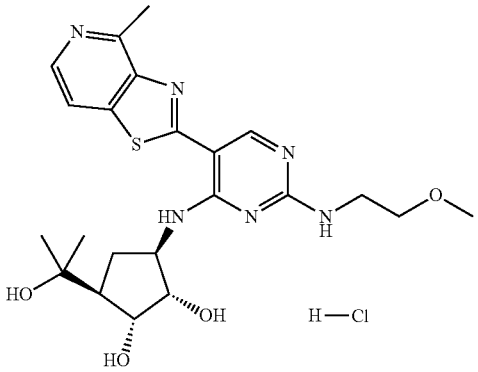
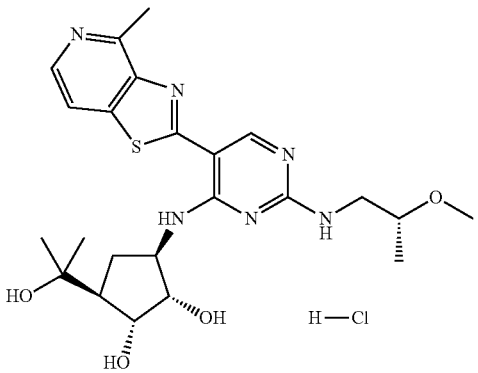
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4936		A	(DMSO-d6) δ 1.06 (s, 3H), 1.18 (s, 3H), 1.22 (t, 3H, J = 7.4 Hz), 1.32-1.43 (m, 1H), 1.78-1.88 (m, 1H), 2.27-2.38 (m, 1H), 2.61 (q, 2H, J = 7.5 Hz), 2.69-2.81 (m, 2H), 3.04 (s, 3H), 3.52-3.74 (m, 1H), 3.72-3.78 (m, 1H), 3.89-3.96 (m, 1H), 4.25-4.35 (m, 1H), 8.38-8.46 (m, 1H), 8.46-8.55 (m, 1H), 8.58 (app d, 1H, J = 6.0 Hz), 8.78 (s, 1H), 9.98 (br s, 1H).	505.2
4937		B	(DMSO-d6) δ 1.06 (s, 3H), 1.18 (s, 3H), 1.33-1.42 (m, 1H), 1.81 (dt, 1H, J = 3.2, 9.1 Hz), 2.24-2.36 (m, 1H), 3.04 (s, 3H), 3.73 (dd, 1H, J = 5.3, 8.5 Hz), 3.93 (dd, 1H, J = 3.3, 5.2 Hz), 4.32-4.42 (m, 1H), 7.97 (br s, 1H), 8.48 (app br d, 1H, J = 5.6 Hz), 8.59 (d, 1H, J = 6.0 Hz), 8.85 (s, 1H), 10.11 (br d, 1H, J = 6.6 Hz).	417.2
4938		A	(DMSO-d6) δ 1.07 (s, 3H), 1.18 (s, 3H), 1.37-1.47 (m, 1H), 1.85 (br dt, 1H, J = 3.5, 8.8 Hz), 2.27-2.39 (m, 1H), 3.52-3.59 (m, 2H), 3.59-3.73 (m, 1H), 3.74-3.80 (m, 2H), 3.90-3.94 (m, 1H), 4.31 (app quint, 1H, J = 7.5 Hz), 8.45-8.52 (m, 1H), 8.54 (app d, 1H, J = 5.9 Hz), 8.60 (app d, 1H, J = 6.0 Hz), 8.85 (s, 1H), 9.57 (br s, 1H), 10.01 (app br d, 1H, J = 4.9 Hz).	475.2
4939		A	(DMSO-d6) δ 1.07 (s, 3H), 1.15 (d, 3H, J = 6.0 Hz), 1.18 (s, 3H), 1.37-1.47 (m, 1H), 1.84 (dt, 1H, J = 3.6, 8.9 Hz), 2.28-2.39 (m, 1H), 3.07 (s, 3H), 3.31 (s, 3H), 3.44-3.54 (m, 2H), 3.57 (app quint, 1H, J = 5.7 Hz), 3.76 (dd, 1H, J = 5.4, 7.7 Hz), 3.90-3.95 (m, 1H), 4.32 (app quint, 1H, J = 7.4 Hz), 8.52-8.62 (m, 1H), 8.55 (d, 1H, J = 6.2 Hz), 8.61 (d, 1H, J = 6.1 Hz), 8.88 (s, 1H), 10.02 (app d, 1H, J = 5.7 Hz).	489.2

TABLE V-continued

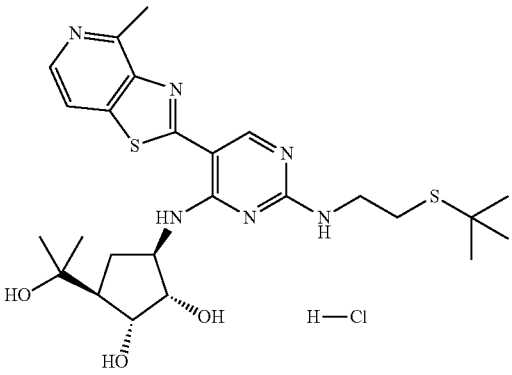
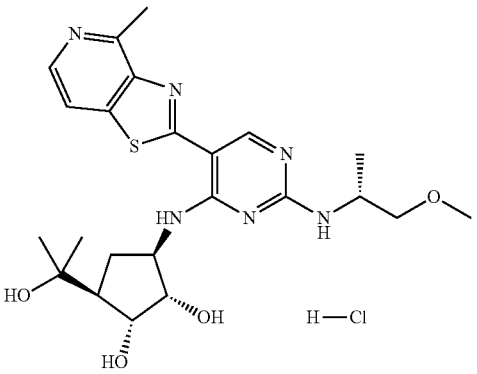
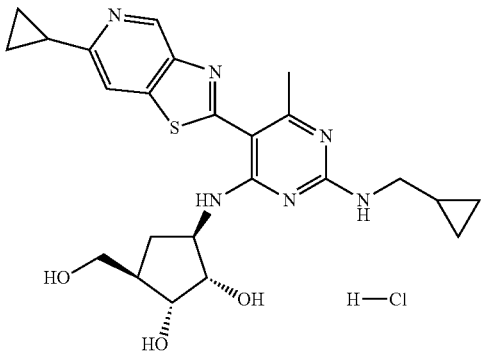
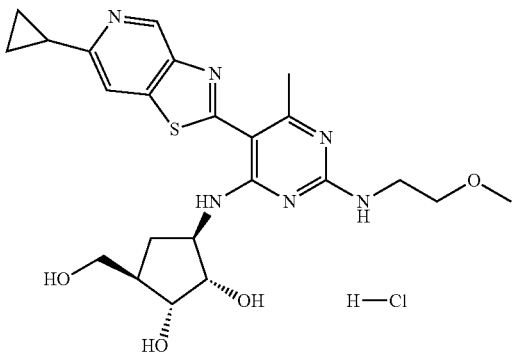
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4940		A	(DMSO-d6) δ 1.06 (s, 3H), 1.18 (s, 3H), 1.31 (s, 9H), 1.33-1.43 (m, 1H), 1.79-1.88 (m, 1H), 2.28-2.39 (m, 1H), 2.72-2.82 (m, 2H), 2.86-2.95 (m, 1H), 3.06 (s, 3H), 3.45-3.61 (m, 1H), 3.61-3.78 (m, 2H), 3.90-3.97 (m, 1H), 4.23-4.34 (m, 1H), 8.04 (br s, 1H), 8.47-8.55 (m, 1H), 8.55-8.64 (m, 1H), 8.82 (s, 1H), 10.03 (br s, 1H).	533.2
4941		A	(DMSO-d6) δ 1.07 (s, 3H), 1.18 (s, 3H), 1.10-1.27 (m, 3H), 1.37-1.48 (m, 1H), 1.80-1.88 (m, 1H), 2.26-2.39 (m, 1H), 3.07 (s, 3H), 3.31 (s, 3H), 3.38-3.74 (m, 2H), 3.75-3.81 (m, 1H), 3.90-3.95 (m, 1H), 4.24-4.36 (m, 2H), 8.48-8.53 (m, 1H), 8.54 (d, 1H, J = 5.9 Hz), 8.60 (d, 1H, J = 5.6 Hz), 8.86 (br s, 1H), 9.97-10.06 (m, 1H).	489.2
4942		A	(DMSO-d6) δ 0.29-0.32 (m, 2H), 0.48-0.54 (m, 2H), 1.01-1.06 (m, 2H), 1.06-1.25 (m, 4H), 1.89-1.99 (m, 1H), 2.14-2.25 (m, 1H), 2.28-2.37 (m, 1H), 2.41 (s, 3H), 3.32-3.42 (m, 4H), 3.68 (t, 1H, J = 4.9 Hz), 3.78 (app t, 1H, J = 5.7 Hz), 4.34-4.42 (m, 1H), 7.99-8.12 (m, 1H), 8.20 (s, 1H), 8.85-9.03 (m, 1H), 9.28 (s, 1H), 13.21 (br s, 1H).	483.2
4943		A	(DMSO-d6) δ 1.00-1.06 (m, 2H), 1.06-1.13 (m, 2H), 1.13-1.24 (m, 1H), 1.88-1.98 (m, 1H), 2.14-2.25 (m, 1H), 2.28-2.37 (m, 1H), 2.40 (s, 3H), 3.31 (s, 3H), 3.33-3.41 (m, 2H), 3.52-3.57 (m, 2H), 3.60-3.66 (m, 1H), 3.68 (app t, 1H, J = 5.0 Hz), 3.78 (app t, 1H, J = 5.8 Hz), 4.39 (app quint, 1H, J = 7.2 Hz), 7.88 (br s, 1H), 8.20 (s, 1H), 8.88-9.01 (m, 1H), 9.28 (s, 1H), 13.13 (br s, 1H).	487.2

TABLE V-continued

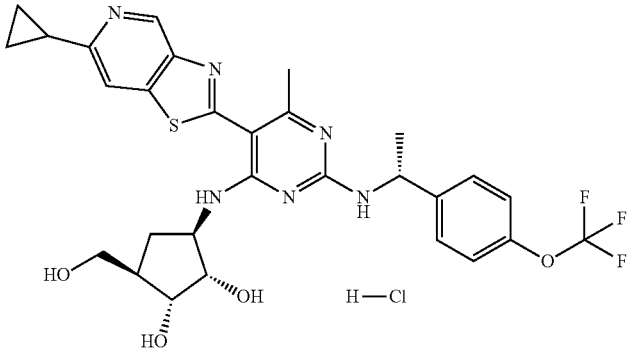
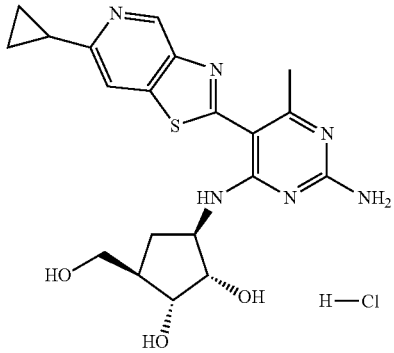
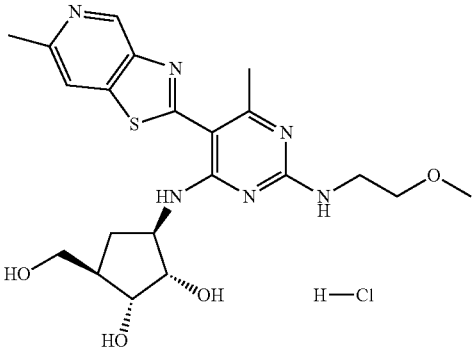
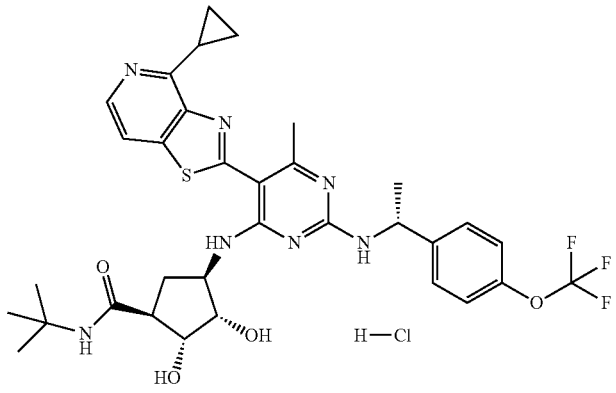
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4944		A	(DMSO-d6) δ 0.89-0.99 (m, 1H), 0.99-1.04 (m, 2H), 1.04-1.11 (m, 2H), 1.55 (d, 3H, J =6.9 Hz), 1.58-1.67 (m, 1H), 1.83-1.92 (m, 1H), 2.26-2.34 (m, 1H), 2.37 (s, 3H), 3.26-3.36 (m, 2H), 3.67 (app t, 1H, J = 4.9 Hz), 3.70-3.75 (m, 1H), 4.29-4.39 (m, 1H), 5.12-5.21 (m, 1H), 7.36 (d, 2H, J = 8.2 Hz), 7.58 (d, 2H, J = 8.6 Hz), 8.17 (s, 1H), 8.62 (app d, 1H, J = 5.9 Hz), 8.83 (app d, 1H, J = 7.4 Hz), 9.25 (s, 1H), 13.03 (br s, 1H).	617.2
4945		A	(DMSO-d6) δ 1.00-1.06 (m, 2H), 1.06-1.12 (m, 2H), 1.10-1.16 (m, 1H), 1.84-1.94 (m, 1H), 2.13 (dt, 1H, J = 8.5, 14.3 Hz), 2.26-2.37 (m, 1H), 2.35 (s, 3H), 3.30-3.39 (m, 2H), 3.63-3.78 (m, 2H), 4.48 (quint, 1H, J = 8.0 Hz), 8.19 (s, 1H), 8.68 (d, 1H, J = 7.8 Hz), 9.27 (s, 1H), 12.96 (br s, 1H).	429.2
4946		A	(DMSO-d6) δ 1.15-1.26 (m, 1H), 1.88-1.99 (m, 1H), 2.16-2.26 (m, 1H), 2.44 (s, 3H), 2.74 (br s, 3H), 3.31 (s, 3H), 3.32-3.42 (m, 2H), 3.52-3.57 (m, 2H), 3.60-3.66 (m, 2H), 3.69 (t, 1H, J = 4.9 Hz), 3.80 (app t, 1H, J = 5.7 Hz), 4.39 (app quint, 1H, J = 7.2 Hz), 7.95 (br s, 1H), 8.39 (br s, 1H), 9.01 (br s, 1H), 9.51 (br s, 1H).	461.2
4947		A	(DMSO-d6) δ 1.05-1.22 (m, 5H), 1.21 (s, 9H), 1.45 (d, 3H, J = 7.1 Hz), 1.97-2.07 (m, 1H), 2.56 (br s, 3H), 2.62-2.70 (m, 1H), 2.97-3.06 (m, 1H), 3.76-3.82 (m, 1H), 3.84-3.90 (m, 1H), 4.18-4.28 (m, 1H), 4.74 (app br s, 1H), 4.82 (app br s, 1H), 5.10-5.20 (m, 1H), 7.30 (app d, 2H, J = 8.2 Hz), 7.40 (s, 1H), 7.55 (d, 2H, J = 8.6 Hz), 7.84 (d, 1H, J = 5.5 Hz), 7.99 (br d, 1H, J = 7.9 Hz), 8.27 (d, 1H, J = 5.3 Hz), 9.78 (br d, 1H, J = 6.3 Hz).	686.3

TABLE V-continued

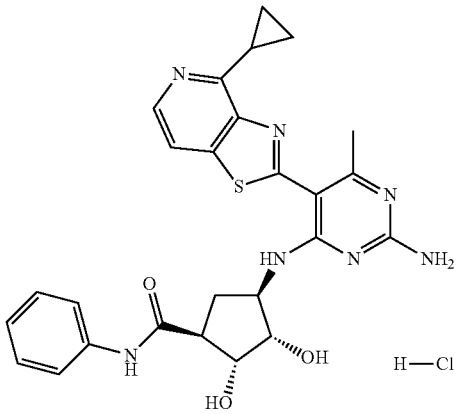
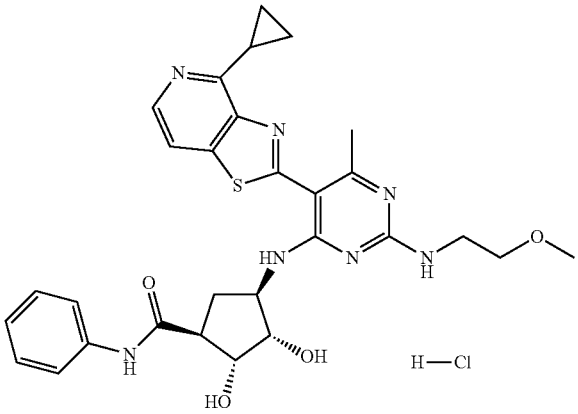
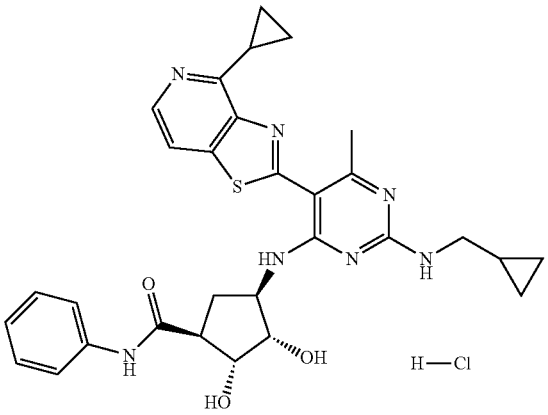
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4948		A	(DMSO-d6) δ 1.25-1.34 (m, 2H), 1.40 (br s, 2H), 1.57 (app quint, 1H, J = 6.7 Hz), 2.35-2.45 (m, 1H), 2.40 (s, 3H), 2.86-2.93 (m, 1H), 3.02-3.10 (m, 1H), 3.86 (app t, 1H, J = 4.9 Hz), 4.00 (t, 1H, J = 4.9 Hz), 4.46-4.56 (m, 1H), 7.01 (t, 1H, J = 7.3 Hz), 7.23 (t, 2H, J = 8.0 Hz), 7.38 (app d, 2H, J = 7.6 Hz), 8.25 (br d, 1H, J = 4.7 Hz), 8.50 (d, 1H, J = 5.9 Hz), 8.87 (br d, 1H, J = 7.0 Hz), 10.17 (br s, 1H).	518.2
4949		A	(DMSO-d6) δ 1.30-1.40 (m, 2H), 1.51 (br s, 2H), 1.56-1.66 (m, 1H), 2.40-2.50 (m, 1H), 2.45 (s, 3H), 2.89-2.97 (m, 1H), 3.04-3.13 (m, 1H), 3.33 (s, 3H), 3.54-3.60 (m, 2H), 3.65-3.72 (m, 2H), 3.90 (app t, 1H, J = 4.4 Hz), 4.01 (t, 1H, J = 5.3 Hz), 4.40-4.49 (m, 1H), 7.02 (t, 1H, J = 7.4 Hz), 7.24 (t, 2H, J = 8.0 Hz), 7.39 (app d, 2H, J = 7.6 Hz), 8.09 (br s, 1H), 8.35 (app br d, 1H, J = 5.5 Hz), 8.53 (d, 1H, J = 6.0 Hz), 9.04 (br s, 1H), 10.19 (br s, 1H).	576.2
4950		A	(DMSO-d6) δ 0.32-0.37 (m, 2H), 0.49-0.55 (m, 2H), 1.11-1.22 (m, 1H), 1.28-1.36 (m, 1H), 1.46 (br s, 2H), 1.56-1.65 (m, 1H), 2.45 (s, 3H), 2.89-2.97 (m, 1H), 3.04-3.12 (m, 1H), 3.40 (app t, 2H, J = 6.4 Hz), 3.90 (app t, 1H, J = 4.3 Hz), 4.02 (t, 1H, J = 5.2 Hz), 4.40-4.49 (m, 2H), 7.02 (t, 1H, J = 7.5 Hz), 7.24 (t, 2H, J = 8.2 Hz), 7.38 (app d, 2H, J = 7.6 Hz), 8.18-8.25 (m, 1H), 8.31 (app br d, 1H, J = 5.1 Hz), 8.52 (d, 1H, J = 5.9 Hz), 9.05 (br s, 1H), 10.16 (s, 1H).	572.2

TABLE V-continued

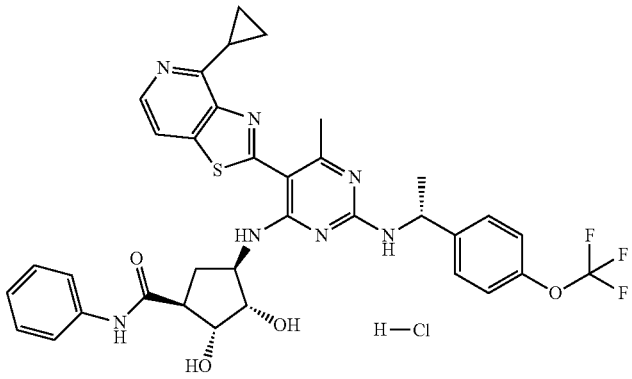
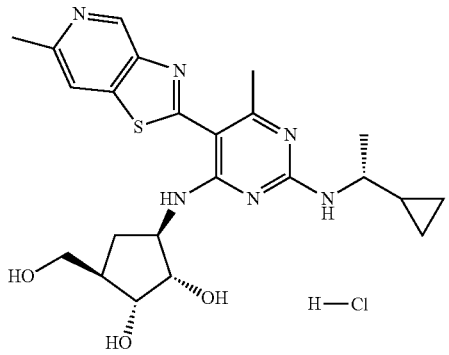
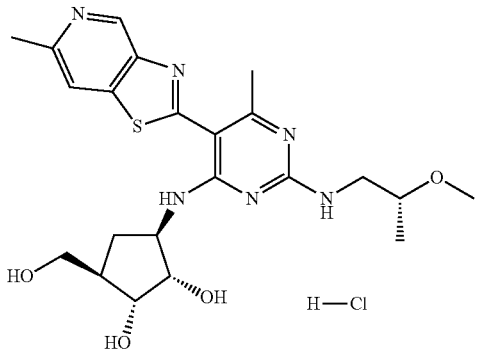
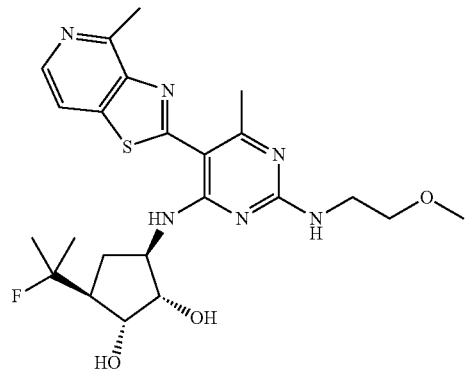
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4951		B	(DMSO-d6, D_2O exchanged) δ 1.28-1.50 (m, 1H), 1.30-1.38 (m, 2H), 1.41-1.48 (m, 2H), 1.59 (d, 3H, J = 7.1 Hz), 1.92-2.03 (m, 1H), 2.43 (s, 3H), 2.88 (app q, 1H, J = 7.3 Hz), 2.88-3.06 (m, 1H), 3.90 (app t, 2H, J = 4.9 Hz), 3.97 (app t, 1H, J = 5.4 Hz), 4.28-4.36 (m, 1H), 5.20-5.29 (m, 1H), 7.04 (t, 1H, J = 7.4 Hz), 7.25 (app t, 2H, J = 7.8 Hz), 7.40 (d, 2H, J = 8.8 Hz), 8.32 (d, 1H, J = 5.9 Hz), 8.51 (d, 1H, J = 6.1 Hz), 10.15 (s, 1H).	706.2
4952		A	(DMSO-d6) δ 0.26-0.33 (m, 1H), 0.36-0.44 (m, 1H), 0.44-0.58 (m 2H), 1.03-1.13 (m, 1H), 1.15-1.28 (m, 1H), 1.31 (d, 3H, J = 6.4 Hz), 1.88-1.99 (m, 1H), 2.12-2.23 (m, 1H), 2.43 (s, 3H), 2.74 (s, 3H), 3.32-3.42 (m, 2H), 3.58-3.69 (m, 1H), 3.69 (t, 1H, J = 5.0 Hz), 3.76-3.83 (m, 1H), 4.26-4.43 (m, 1H), 8.41-8.44 (m, 1H), 8.38 (s, 1H), 9.00 (br s, 1H), 9.49 (s, 1H), 13.16 (br s, 1H).	471.2
4953		A	(DMSO-d6) δ 1.15 (d, 3H, J = 6.0 Hz), 1.17-1.31 (m, 1H), 1.88-1.98 (m, 1H), 2.16-2.29 (m, 1H), 2.44 (s, 3H), 2.74 (s, 3H), 3.31 (s, 1H), 3.34-3.42 (m, 2H), 3.43-3.62 (m, 3H), 3.69 (t, 1H, J = 4.9 Hz), 3.77-3.82 (m, 1H), 4.40 (app quint, 2H, J = 7.4H), 7.99 (s, 1H), 8.39 (s, 1H), 9.02 (d, 1H, J = 7.0 Hz), 9.50 (s, 1H), 13.34 (br s, 1H).	475.2
4954		A	(DMSO-d6) δ 1.40 (d, 3H, J = 21.1 Hz), 1.88-1.99 (d, 3H, J = 20.9 Hz), 1.76-1.87 (m, 1H), 2.18-2.27 (m, 1H), 2.27-2.38 (m, 1H), 2.73 (s, 3H), 2.94 (s, 3H), 3.26 (br s, 1H), 3.40 (s, 3H), 3.57-3.62 (m, 2H), 3.63 (br s, 2H), 3.83-3.90 (m, 1H), 4.15 (dd, 1H, J = 2.7, 6.3 Hz), 4.42 (br s, 1H), 5.53 (br s, 1H), 6.71 (br s, 1H), 7.66 (d, 1H, J = 5.4 Hz), 8.38 (d, 1H, J = 5.5 Hz), 10.62 (br s, 1H).	491.2

TABLE V-continued

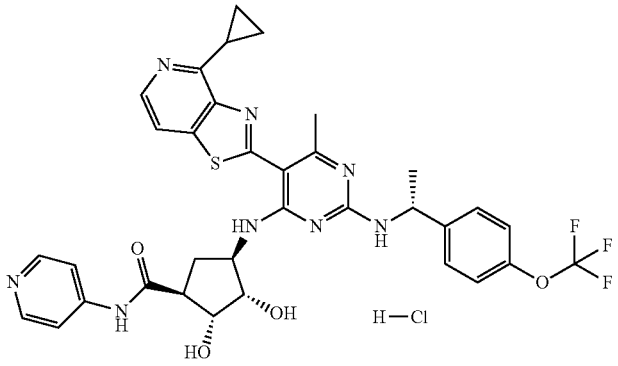
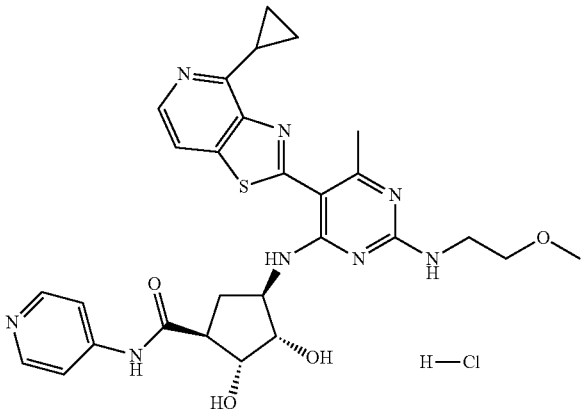
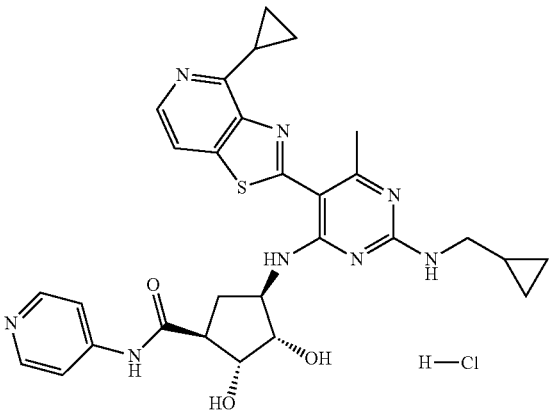
Compd #	Structure	EC90 (uM) range	1H NMR data	MS (M + H)+
4955		A	(DMSO-d6 mixt. of isomers) δ 1.06-1.20 (m, 4H), 1.25 and 1.46 (d's, 3H, J = 6.9 Hz), 2.10-2.20 (m, 1H), 2.57 (s, 3H), 2.94 (app q, 1H, J = 8.2 Hz), 2.96-3.05 (m, 1H), 3.82-3.90 (m, 1H), 4.02-4.10 (m, 1H), 4.20-4.27 (m, 1H), 5.00 (br d, 1H, J = 4.1 Hz), 5.04 (br d, 1H, J = 5.3 Hz), 5.12-5.22 (m, 1H), 7.29 (app t, 2H, J = 9.0 Hz), 7.48-7.58 (m, 4H), 7.86 (d, 1H, J = 5.3 Hz), 7.98-8.03 (m, 1 Hz), 8.29 (d, 1H, J = 5.3 Hz), 8.41 (app d, 2H, J = 6.5 Hz), 10.40 (s, 1H).	707.2
4956		A	(DMSO-d6) δ 1.36-1.44 (m, 2H), 1.58 (br s, 2H), 1.64-1.74 (m, 1H), 2.40-2.58 (m, 1H), 2.47 (s, 3H), 3.04-3.13 (m, 1H), 3.14-3.22 (m, 1H), 3.23 (s, 3H), 3.52-3.61 (m, 2H), 3.62-3.72 (m, 2H), 3.90 (app t, 1H, J = 5.0 Hz), 4.10 (t, 1H, J = 5.6 Hz), 4.40-4.51 (m, 1H), 8.13 (br d, 2H, J = 7.3 Hz), 8.39 (br d, 1H, J = 4.9 Hz), 8.51 (d, 1H, J = 6.0 Hz), 8.71 (d, 2H, J = 6.0 Hz), 9.03 (br s, 1H), 12.18 (br s, 1H).	577.2
4957		A	(DMSO-d6) δ 0.32-0.37 (m, 2H), 0.47-0.55 (m, 2H), 1.11-1.22 (m, 1H), 1.28-1.38 (m, 2H), 1.45 (br s, 2H), 1.65-1.75 (m, 1H), 2.48 (s, 3H), 2.40-2.57 (m, 1H), 3.03-3.11 (m, 1H), 3.16 (dt, 1H, J = 6.4, 8.7 Hz), 3.37-3.43 (m 2H), 3.90 (app t, 1H, J = 4.5 Hz), 4.09 (app t, 1H, J = 5.6 Hz), 4.42-4.51 (m, 1H), 8.10 (d, 2H, J = 6.7 Hz), 8.21-8.36 (m, 2H, 2H), 8.49 (d, 1H, J = 5.9 Hz), 8.71 (d, 2H, J = 7.2 Hz), 9.11 (br s, 1H), 12.0 (s, 1H).	573.2

TABLE VI

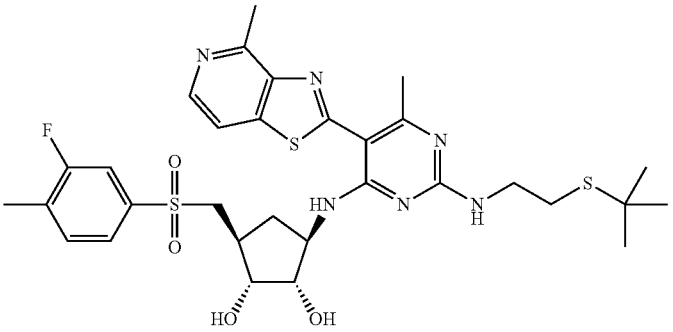
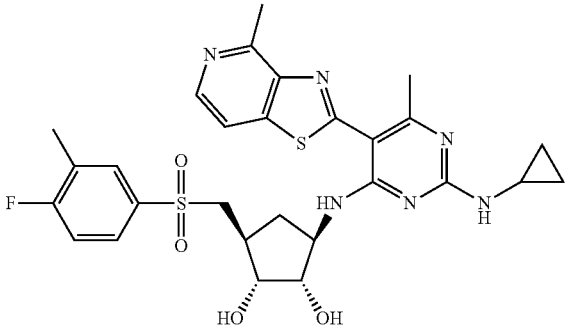
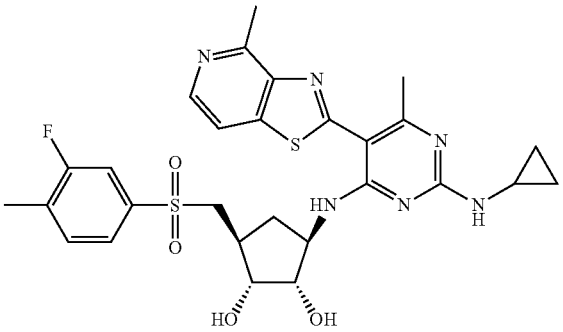
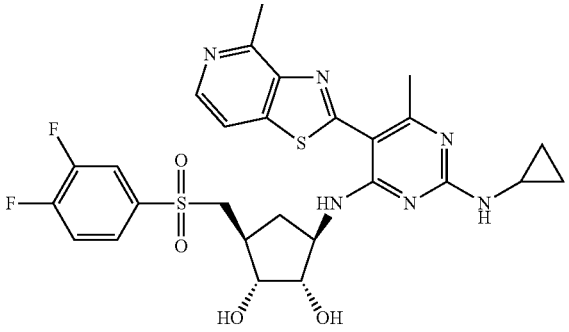
Compd #	Structure	EC90 (μM)	LC-MS or MS
5001		A	675.54
5002		A	599.45
5003		A	599.2
5004		A	603.2

TABLE VI-continued

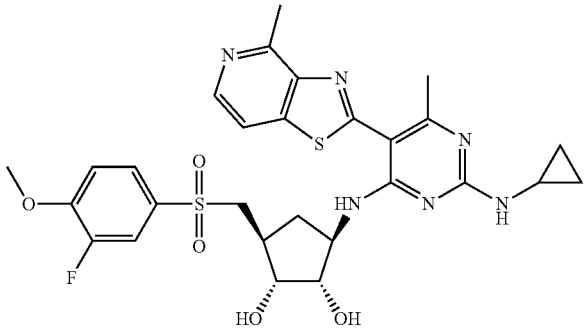
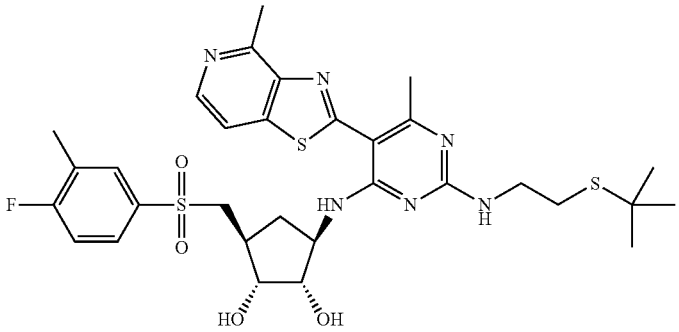
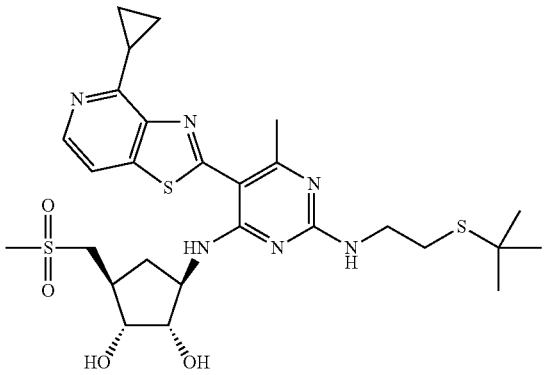
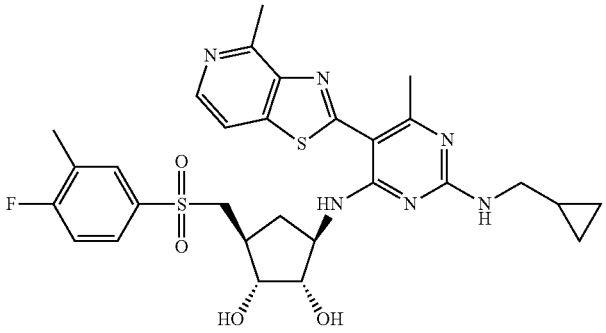
Compd #	Structure	EC90 (μM)	LC-MS or MS
5005		A	615.42
5006		A	675.54
5007		A	607.82
5008		A	613.2

TABLE VI-continued

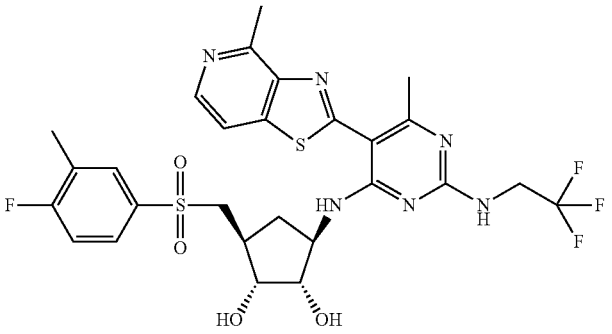
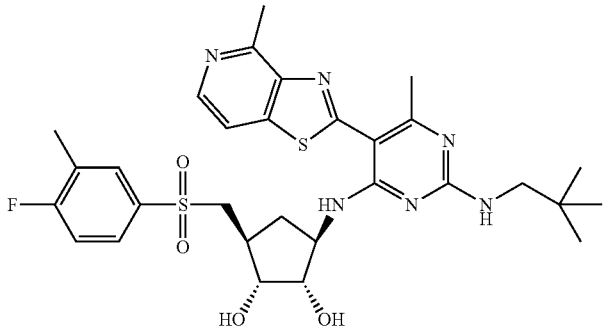
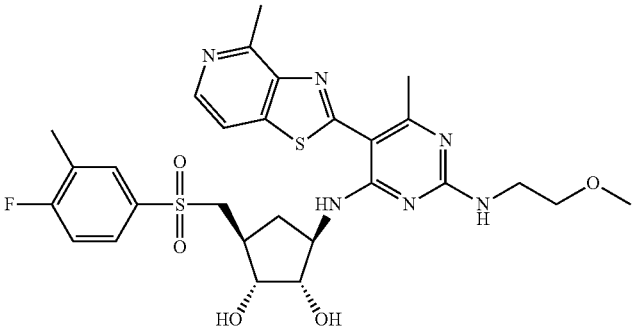
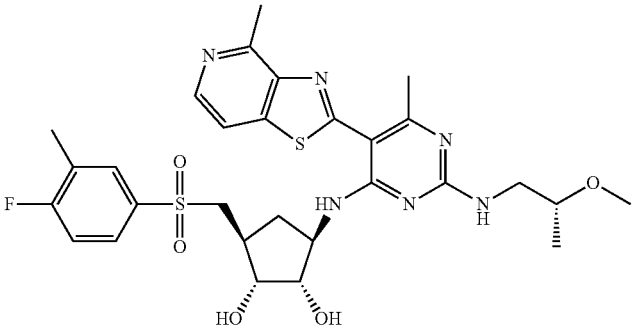
Compd #	Structure	EC90 (μM)	LC-MS or MS
5009		A	641.2
5010		A	629.2
5011		A	617.2
5012		A	631.2

TABLE VI-continued

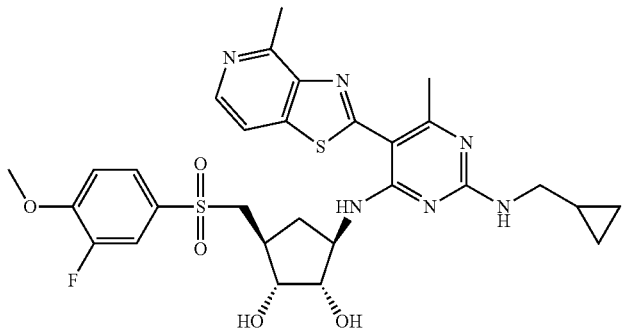
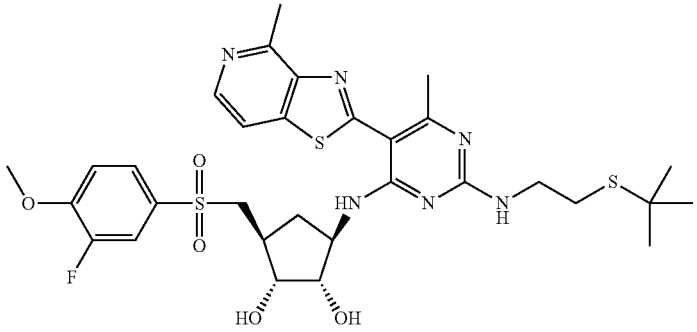
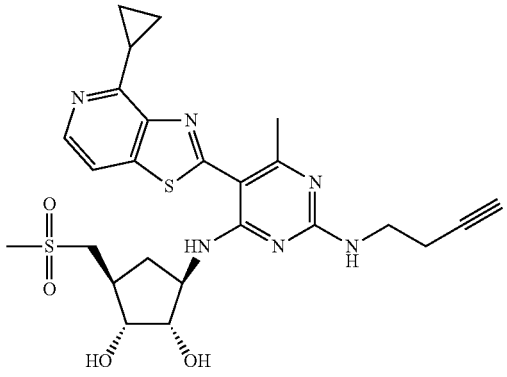
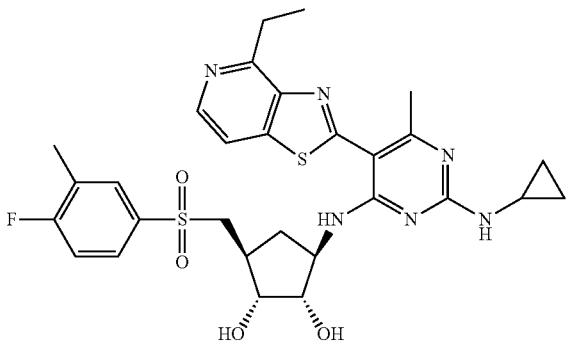
Compd #	Structure	EC90 (μM)	LC-MS or MS
5013		A	629.2
5014		A	691.2
5015		A	543.27
5016		A	613.44

TABLE VI-continued

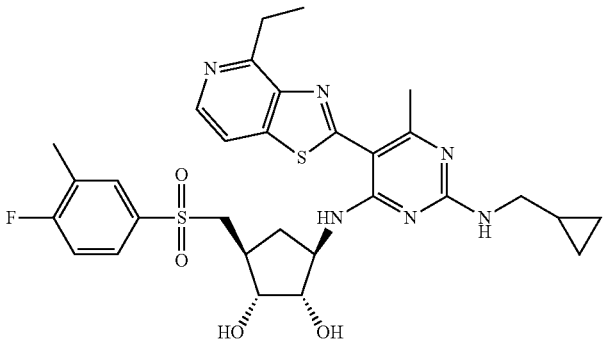
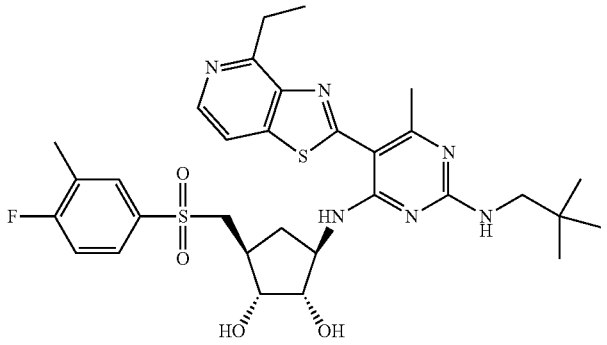
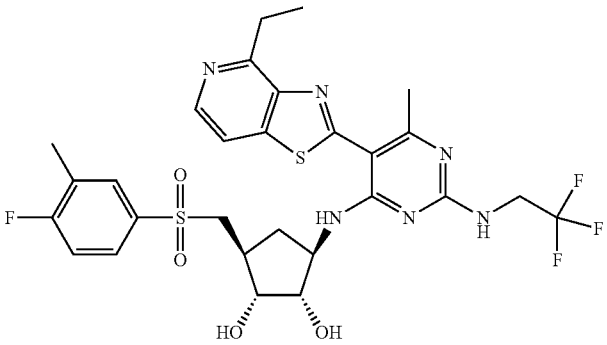
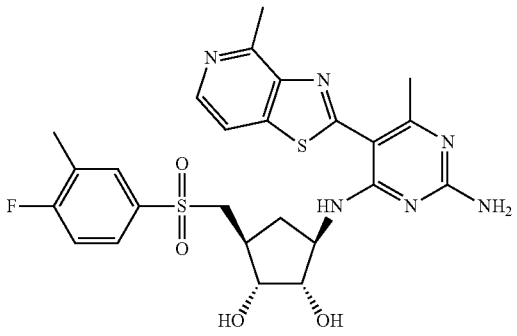
Compd #	Structure	EC90 (μM)	LC-MS or MS
5017		A	627.46
5018		A	643.49
5019		A	655.44
5020		A	559.33

TABLE VI-continued

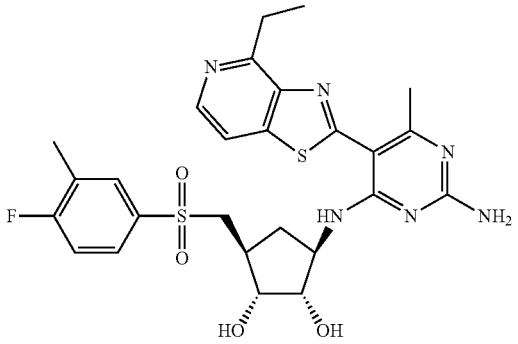
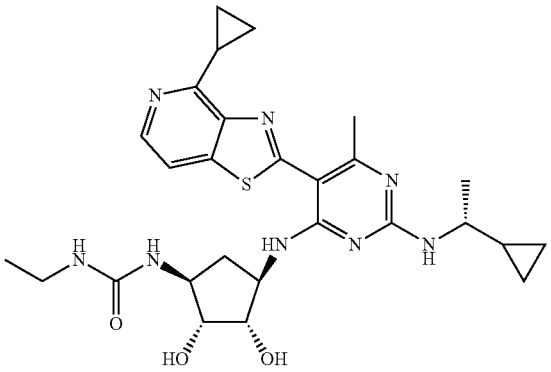
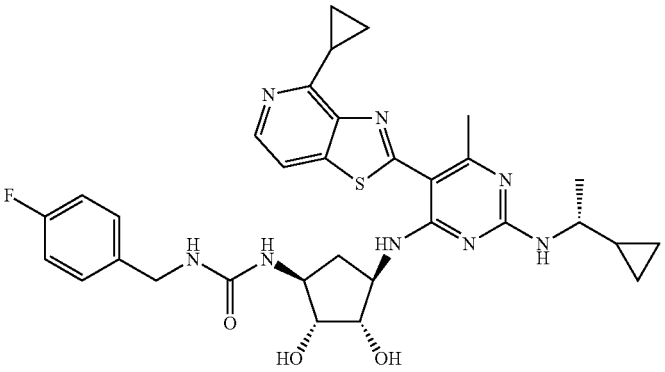
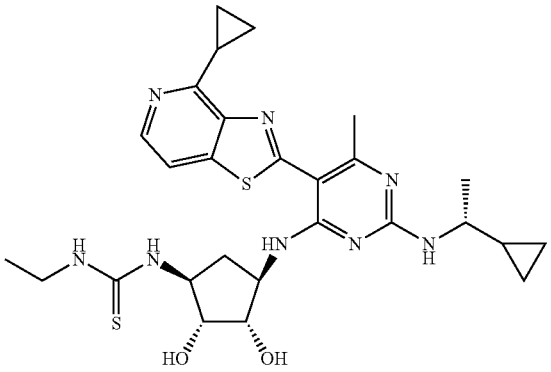
Compd #	Structure	EC90 (μM)	LC-MS or MS
5021		A	573.40
5022		A	553.2
5023		A	633.2
5024		A	569.2

TABLE VI-continued

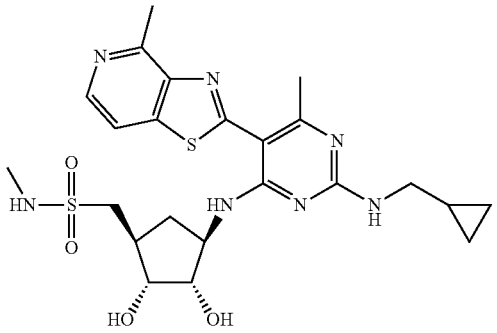
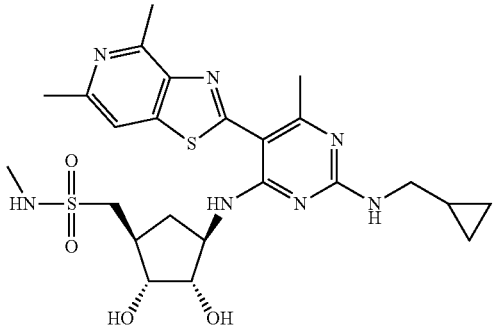
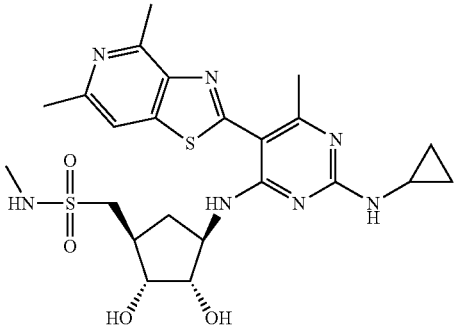
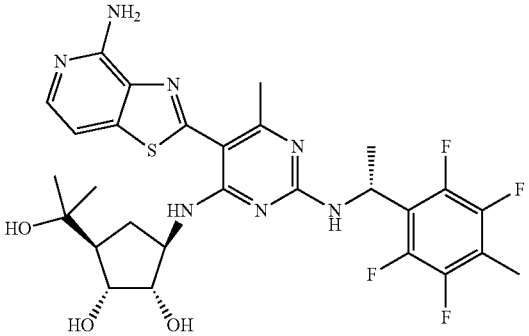
Compd #	Structure	EC90 (μM)	LC-MS or MS
5025		A	534.0
5026		A	548.0
5027		A	534.0
5028		A	622.1

TABLE VI-continued

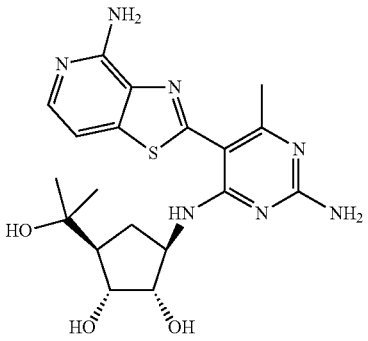
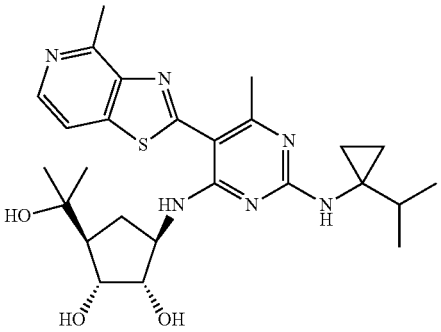
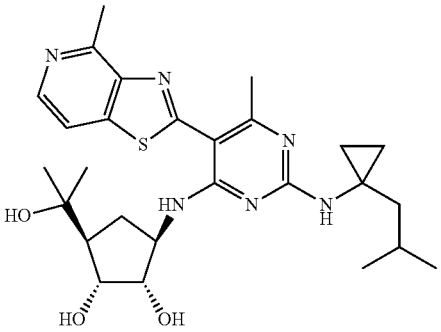
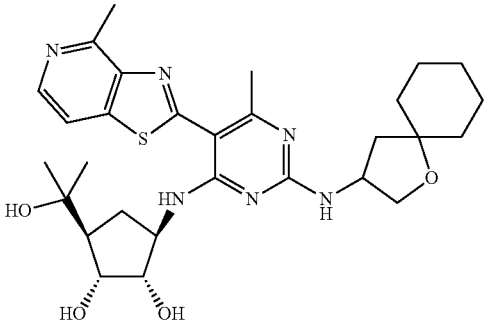
Compd #	Structure	EC90 (μM)	LC-MS or MS
5029		A	432.1
5030		B	513.3
5031		B	527.3
5032		A	569.3

TABLE VI-continued

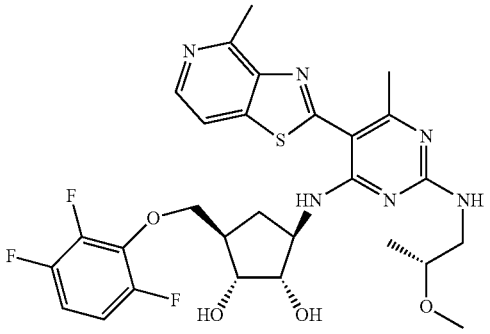
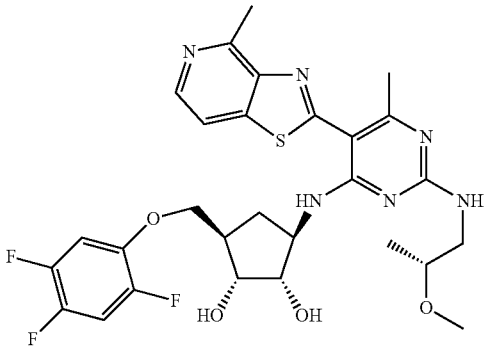
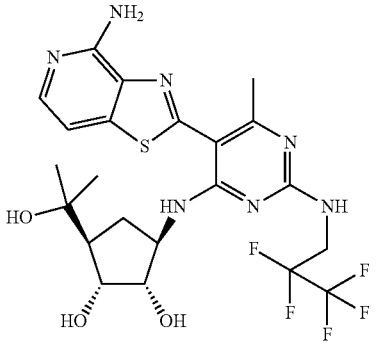
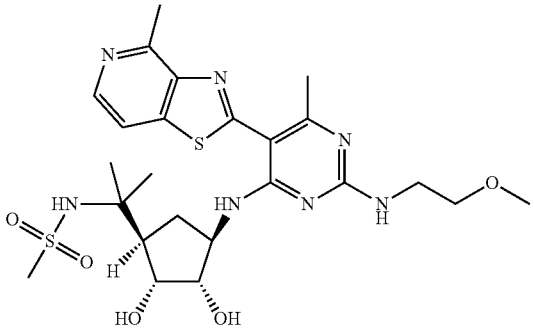
Compd #	Structure	EC90 (μM)	LC-MS or MS
5033		A	605.2
5034		A	605.2
5035		A	564.1
5036		A	566.3

TABLE VI-continued

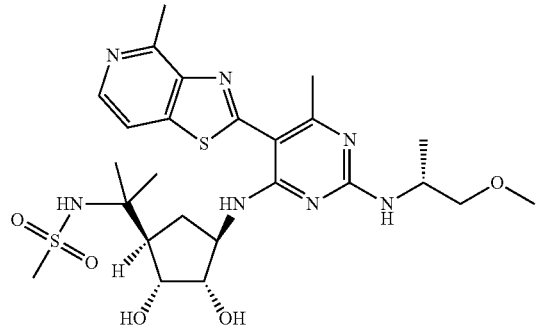
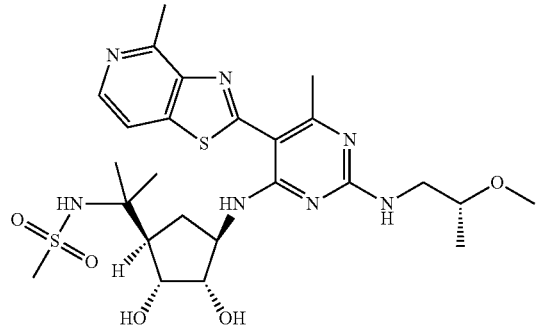
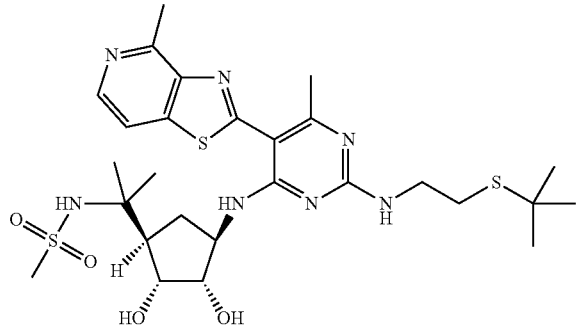
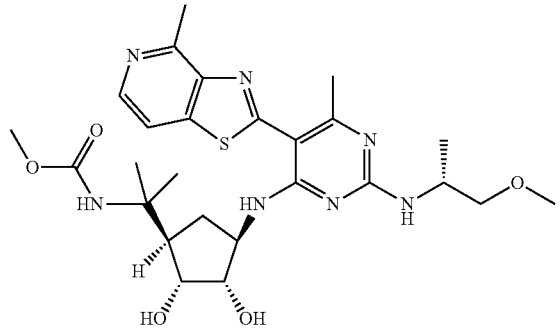
Compd #	Structure	EC90 (μM)	LC-MS or MS
5037		A	580.44
5038		A	580.2
5039		A	624.2
5040		A	560.2

TABLE VI-continued

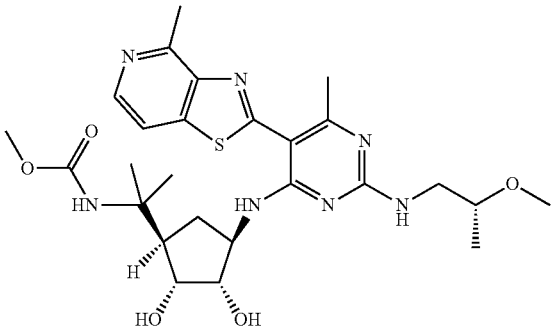
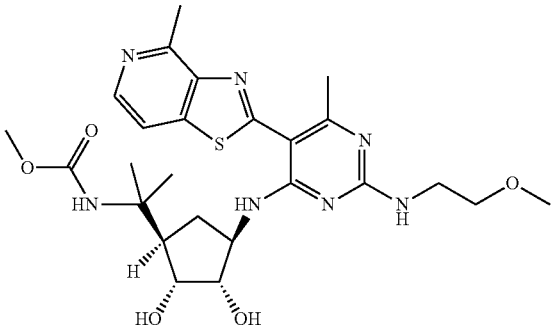
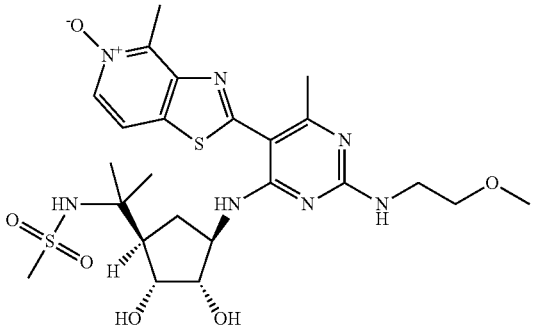
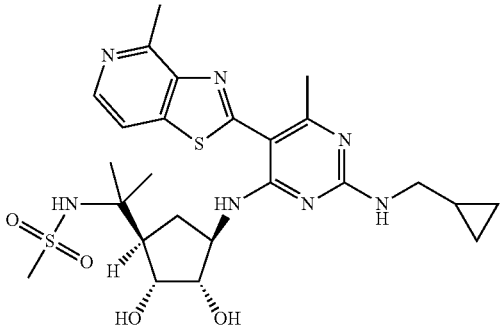
Compd #	Structure	EC90 (μM)	LC-MS or MS
5041		A	560.2
5042		A	546.2
5043		B	582.2
5044		A	562.2

TABLE VI-continued

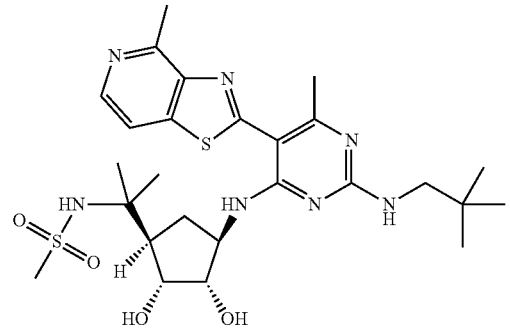
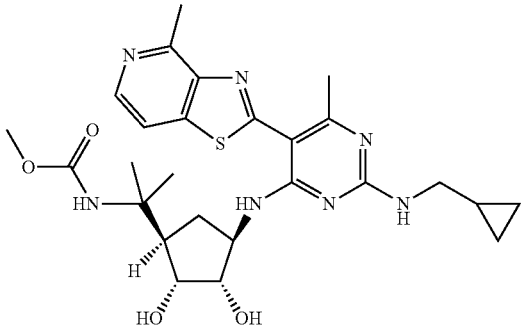
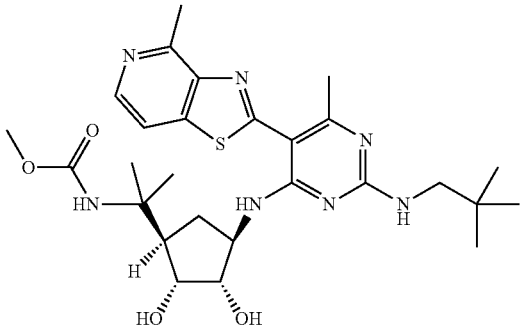
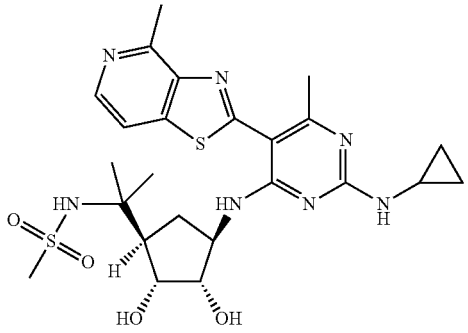
Compd #	Structure	EC90 (μM)	LC-MS or MS
5045		A	578.2
5046		A	542.2
5047		A	558.2
5048		A	548.3

TABLE VI-continued

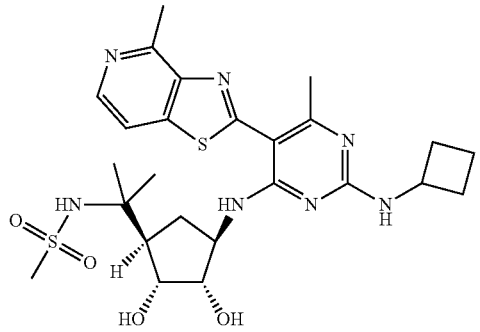
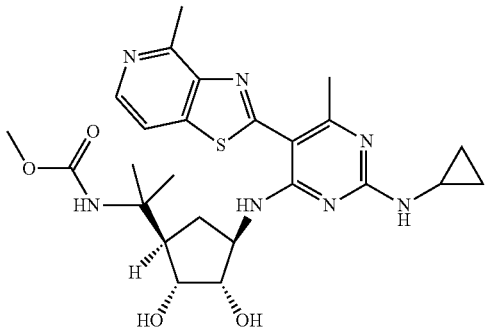
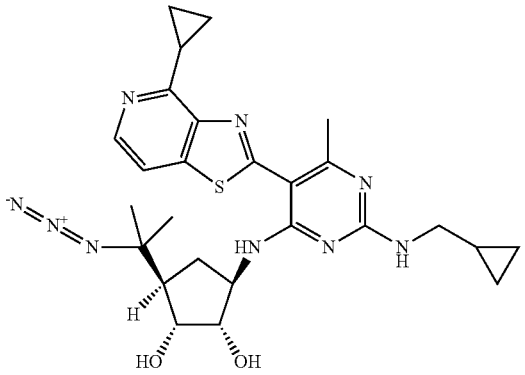
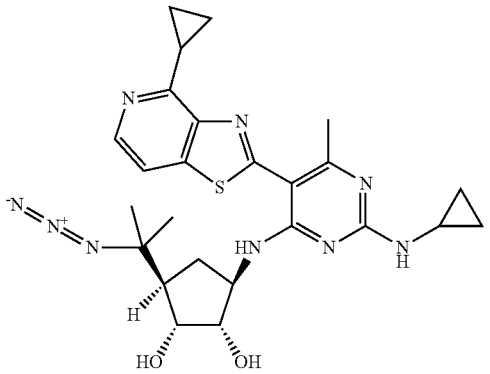
Compd #	Structure	EC90 (μM)	LC-MS or MS
5049		A	563.2
5050		A	528.2
5051		A	536.2
5052		A	522.2

TABLE VI-continued

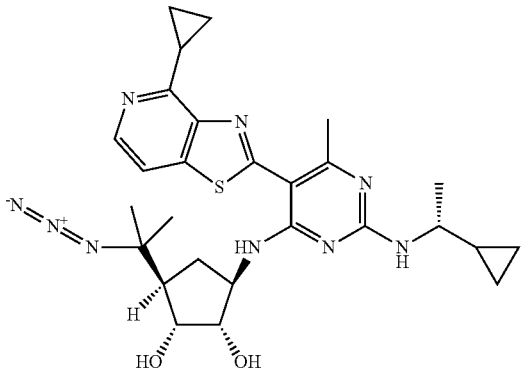
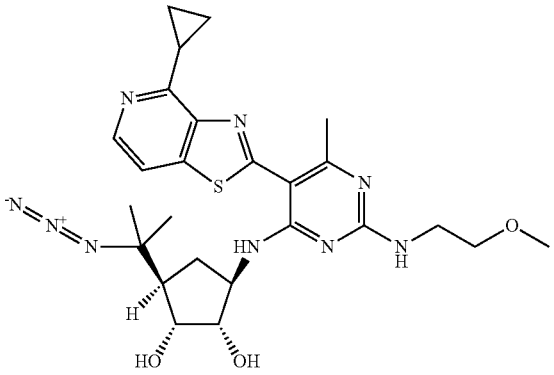
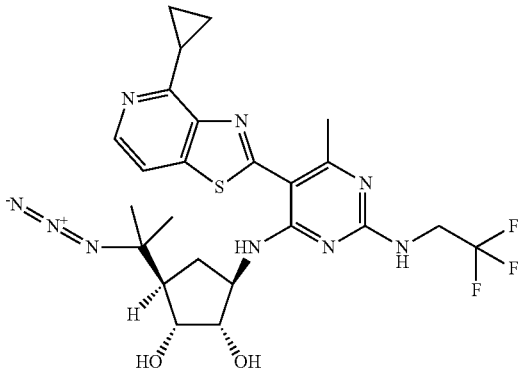
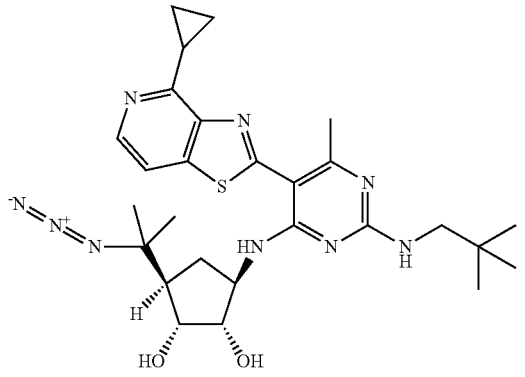
Compd #	Structure	EC90 (μM)	LC-MS or MS
5053		A	550.2
5054		A	540.2
5055		A	564.2
5056		A	552.2

TABLE VI-continued

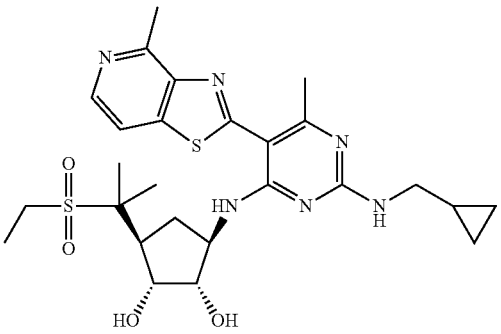
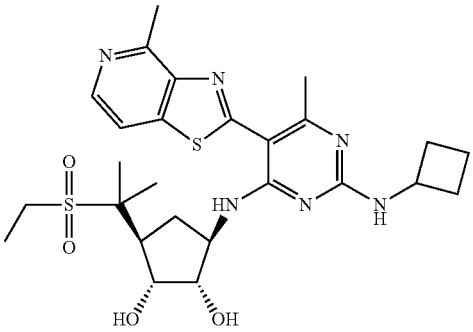
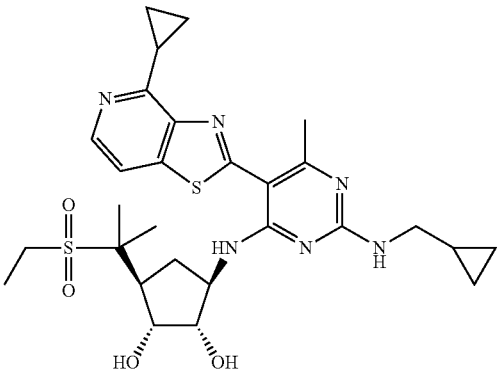
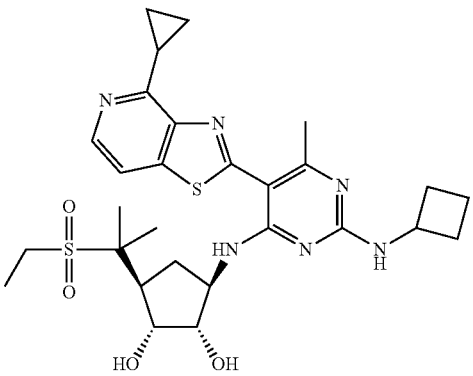
Compd #	Structure	EC90 (μM)	LC-MS or MS
5057		A	561.2
5058		A	561.2
5059		A	587.2
5060		A	587.2

TABLE VI-continued

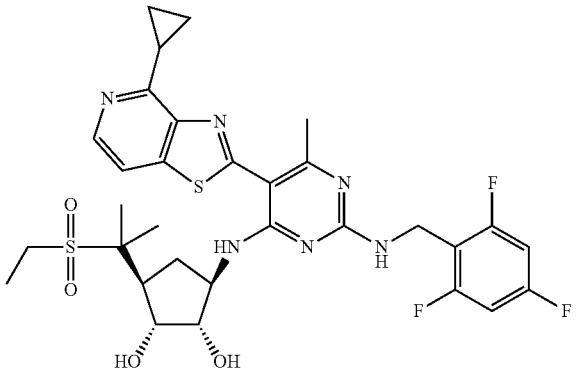
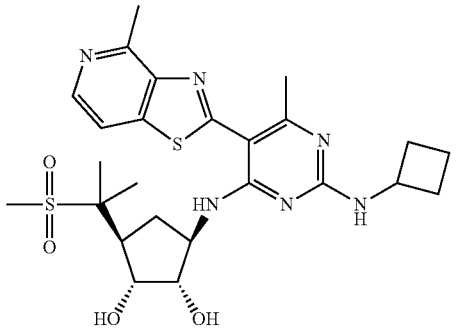
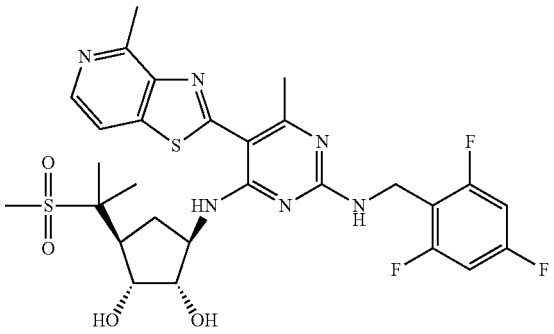
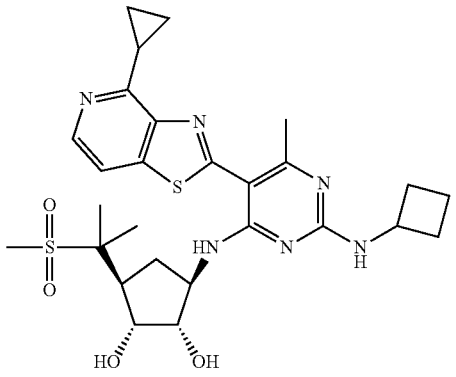
Compd #	Structure	EC90 (μM)	LC-MS or MS
5061		A	677.2
5062		A	547.2
5063		A	637.2
5064		A	573.2

TABLE VI-continued

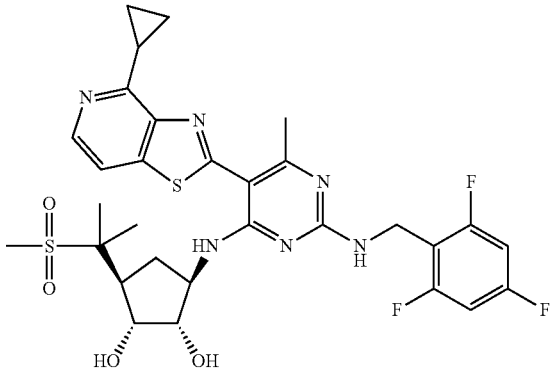
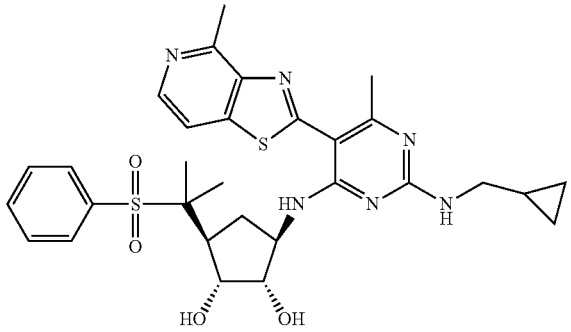
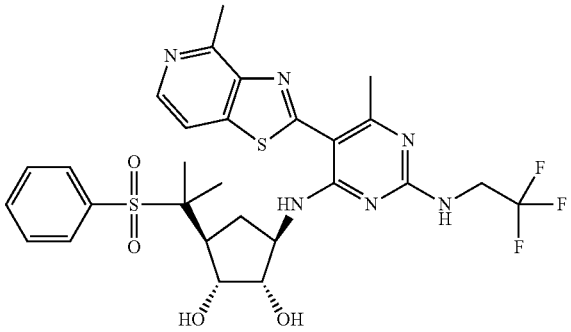
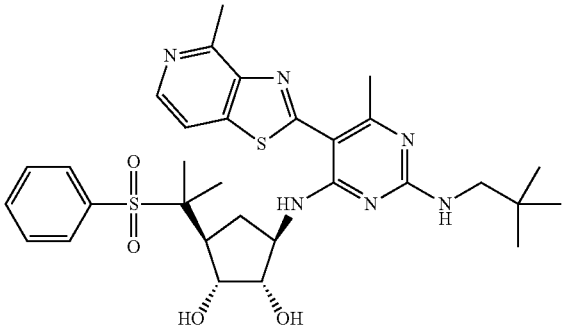
Compd #	Structure	EC90 (μM)	LC-MS or MS
5065		A	663.2
5066		A	609.2
5067		A	637.2
5068		A	625.2

TABLE VI-continued

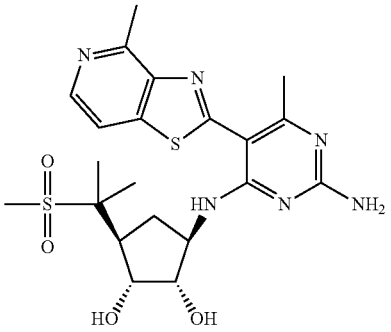
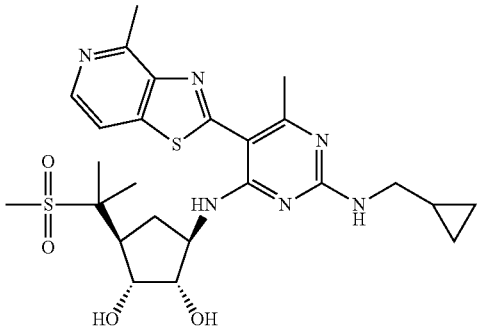
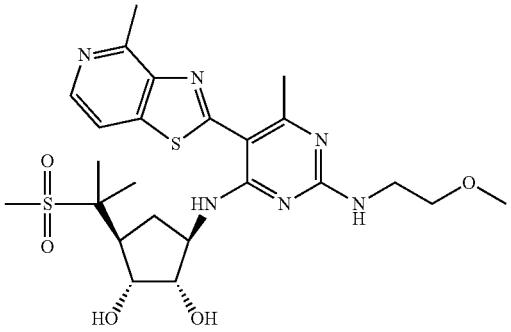
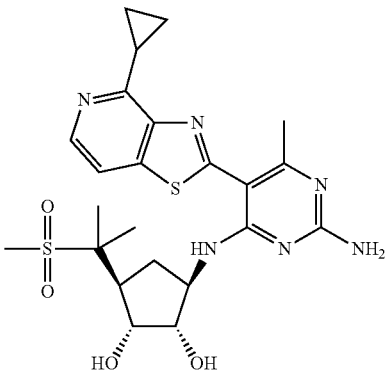
Compd #	Structure	EC90 (μM)	LC-MS or MS
5069		A	493.3
5070		A	547.0
5071		A	551.4
5072		A	519.4

TABLE VI-continued

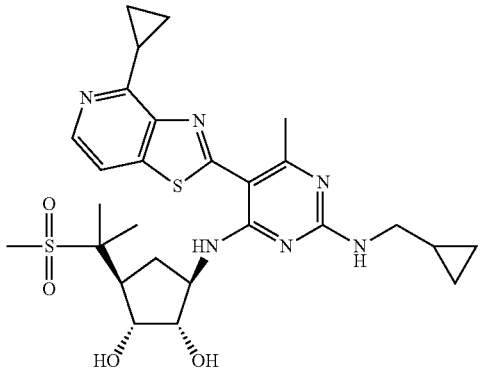
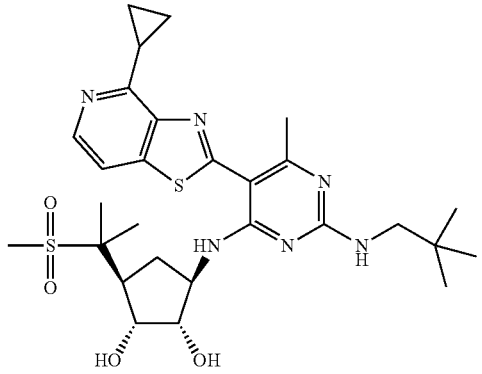
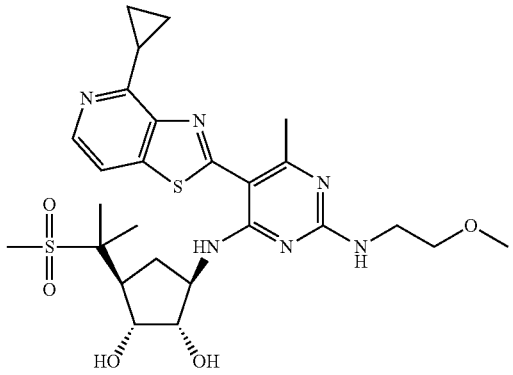
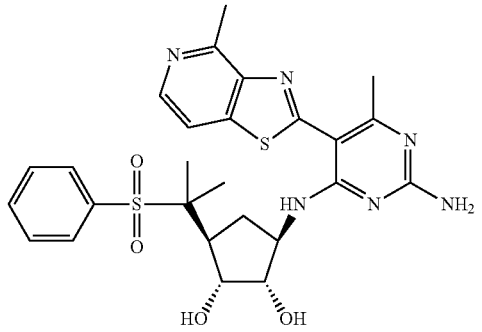
Compd #	Structure	EC90 (μM)	LC-MS or MS
5073		A	573.0
5074		A	589.0
5075		A	577.0
5076		A	555.0

TABLE VI-continued

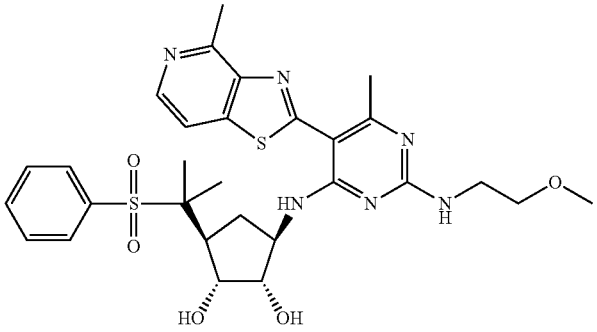
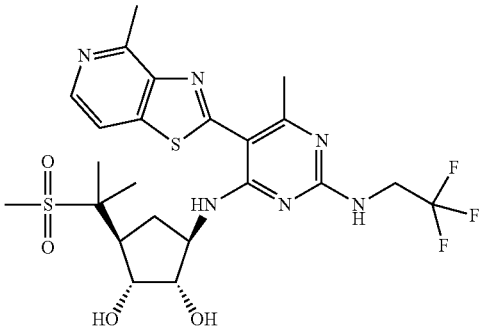
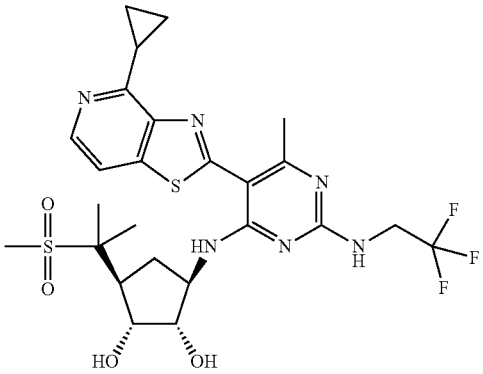
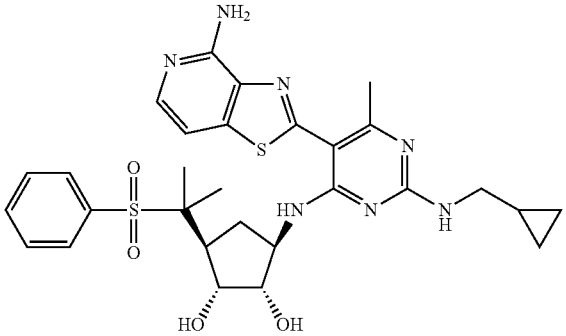
Compd #	Structure	EC90 (μM)	LC-MS or MS
5077		A	613.0
5078		A	575.0
5079		A	601.0
5080		A	610.0

TABLE VI-continued

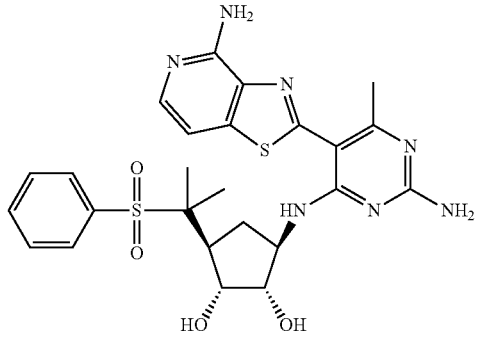
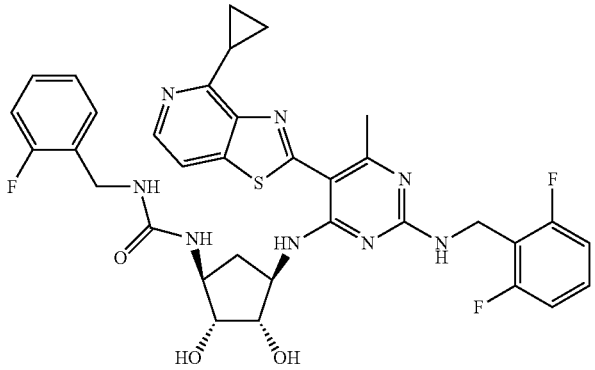
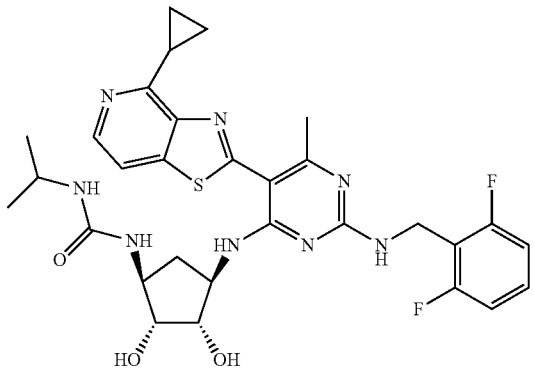
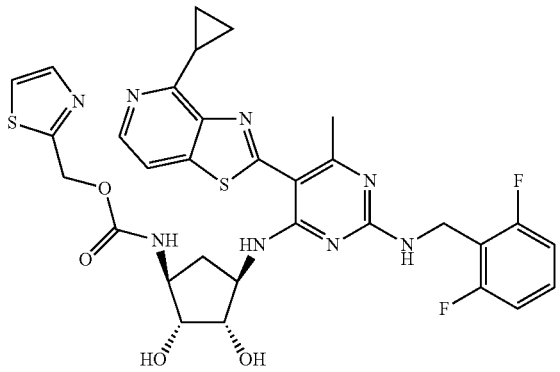
Compd #	Structure	EC90 (μM)	LC-MS or MS
5081		A	556.0
5082		B	690.8
5083		A	625.0
5084		A	681.8

TABLE VI-continued

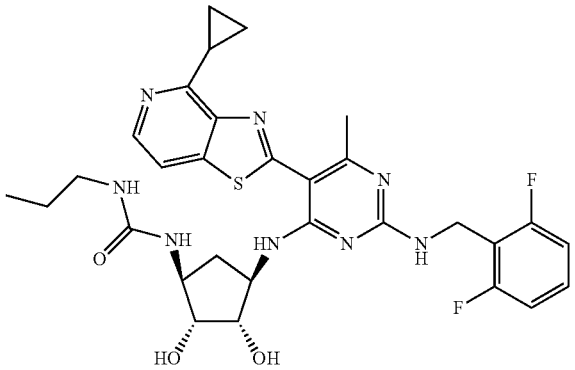
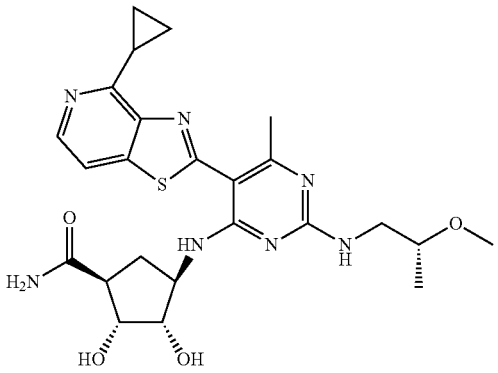
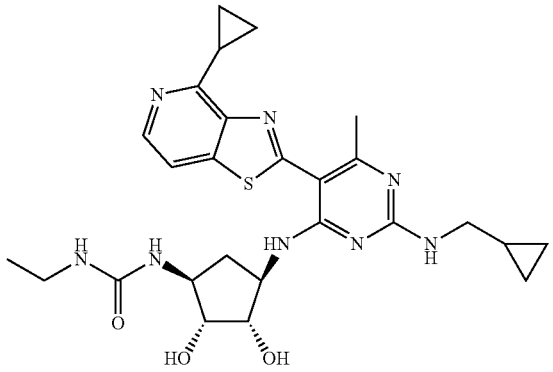
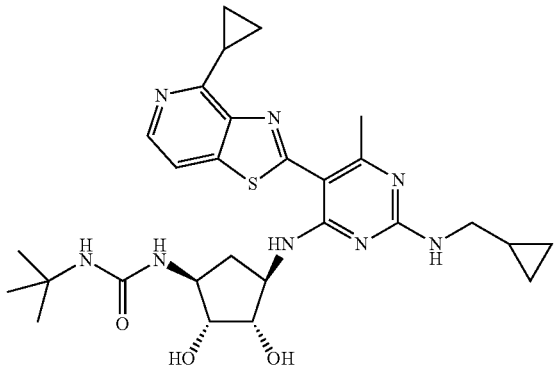
Compd #	Structure	EC90 (μM)	LC-MS or MS
5085		A	626.0
5086		A	514.2
5087		A	539.2
5088		A	567.2

TABLE VI-continued

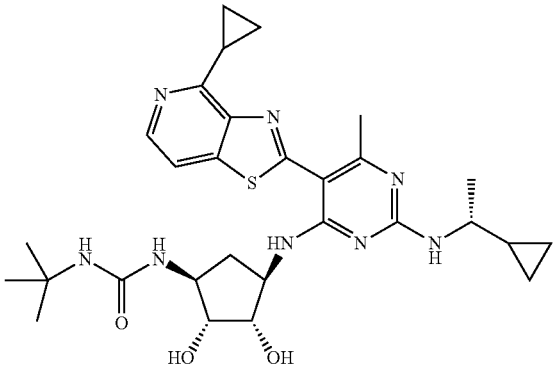
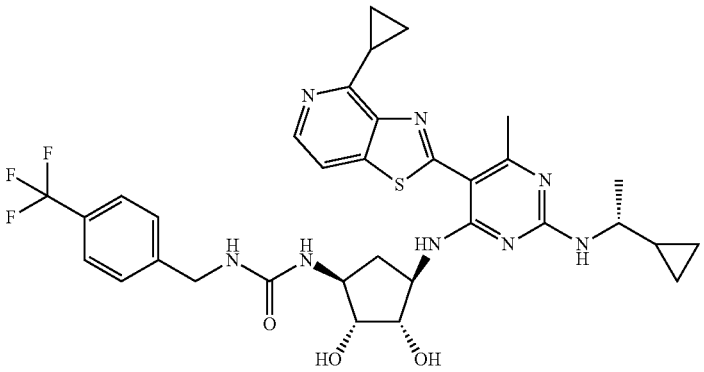
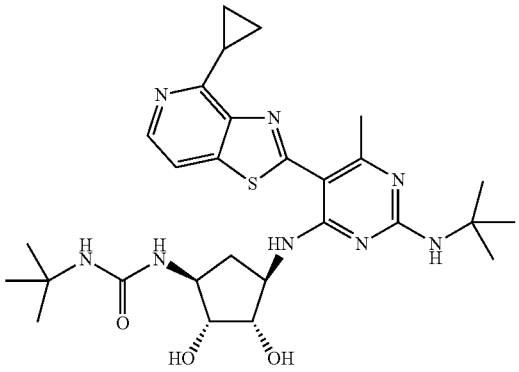
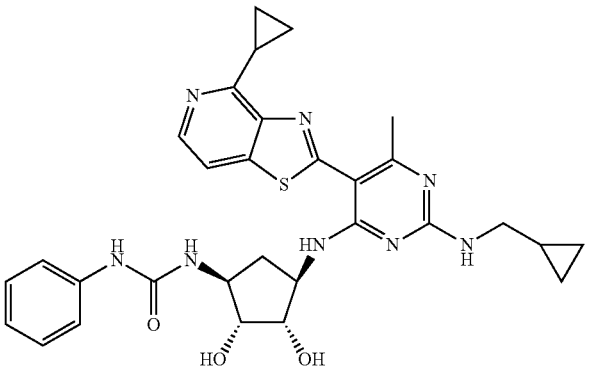
Compd #	Structure	EC90 (μM)	LC-MS or MS
5089		A	581.2
5090		A	683.2
5091		A	569.3
5092		A	587.2

TABLE VI-continued

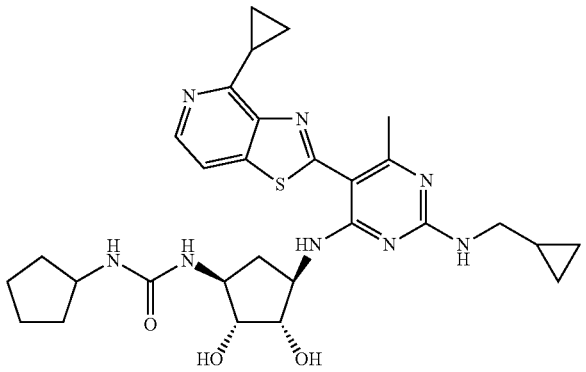
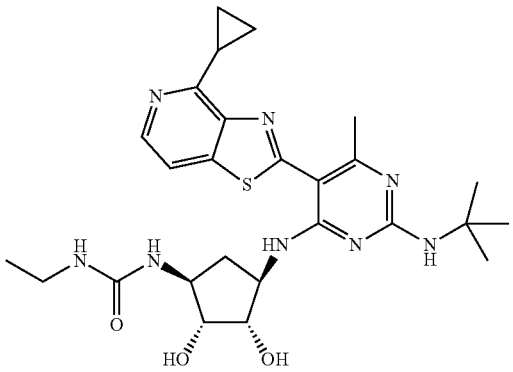
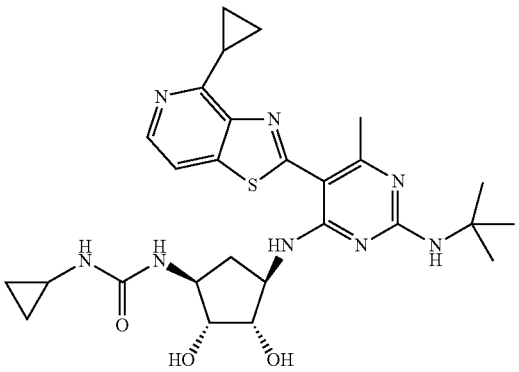
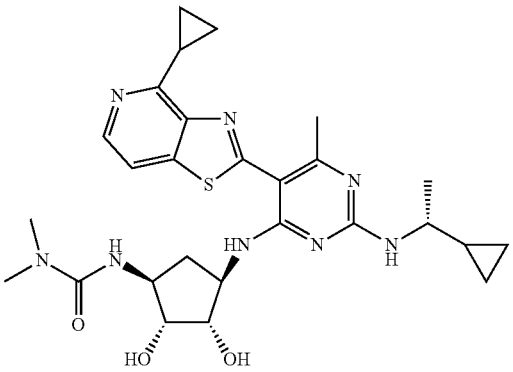
Compd #	Structure	EC90 (μM)	LC-MS or MS
5093		A	579.2
5094		A	541.2
5095		A	553.2
5096		A	553.2

TABLE VI-continued

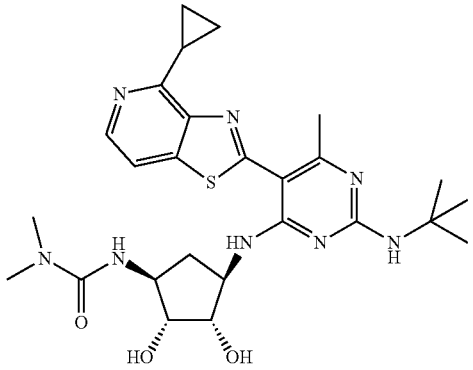
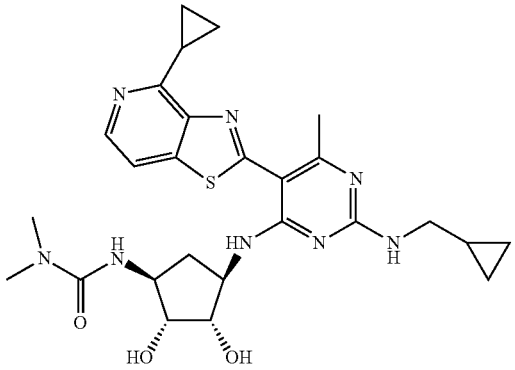
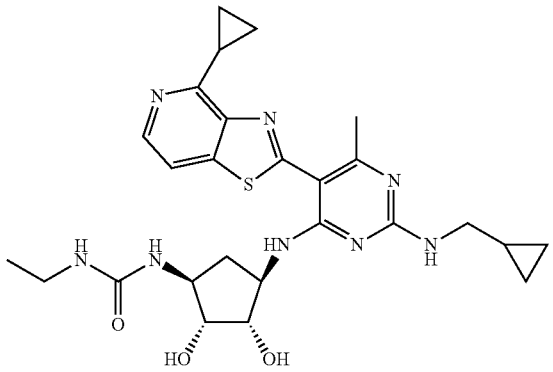
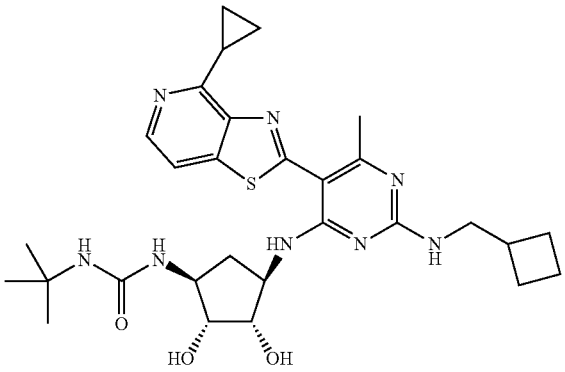
Compd #	Structure	EC90 (μM)	LC-MS or MS
5097		A	541.2
5098		A	539.0
5099		A	555.0
5100		A	581.0

TABLE VI-continued

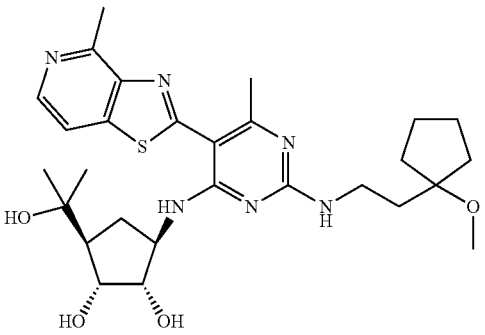
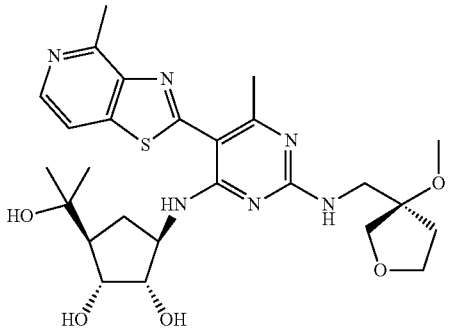
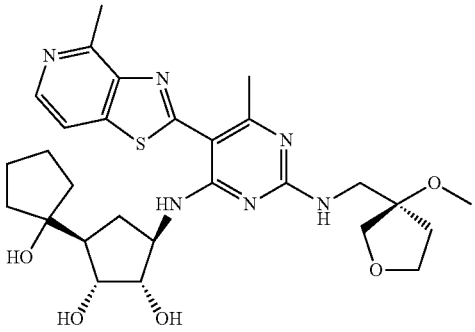
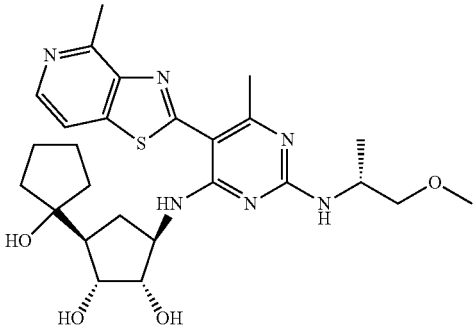
Compd #	Structure	EC90 (μM)	LC-MS or MS
5101		A	557.3
5102		A	545.3
5103		A	571.7
5104		A	529.7

TABLE VI-continued

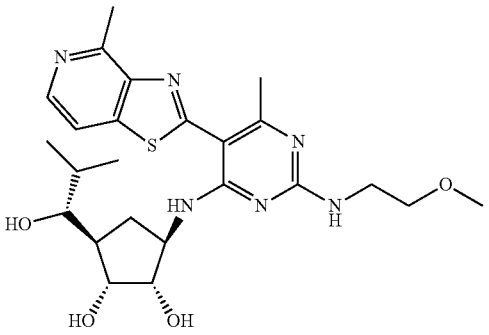
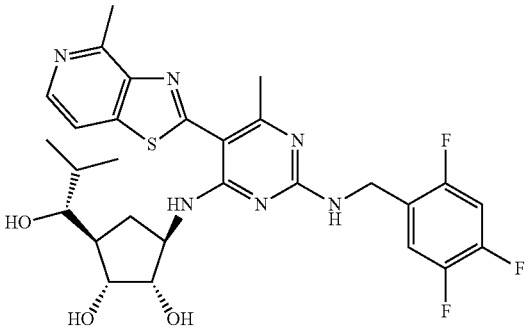
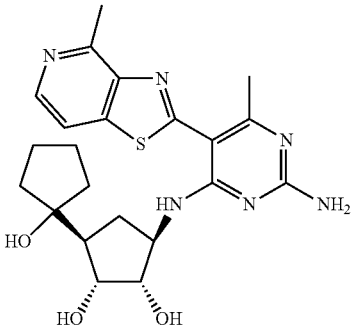
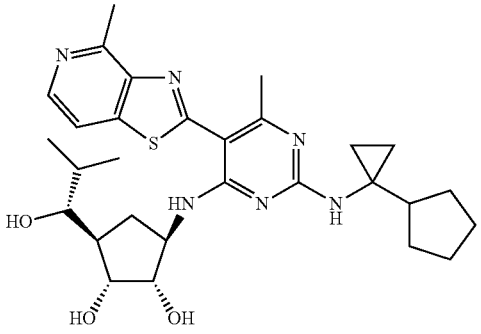
Compd #	Structure	EC90 (μM)	LC-MS or MS
5105		A	503.7
5106		A	589.7
5107		A	457.7
5108		A	553.7

TABLE VI-continued

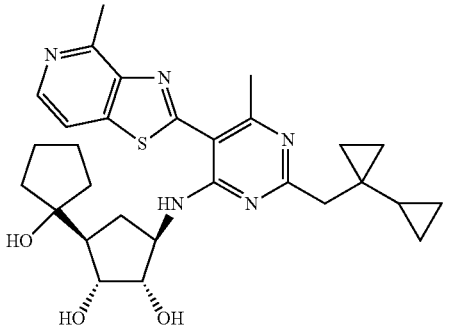
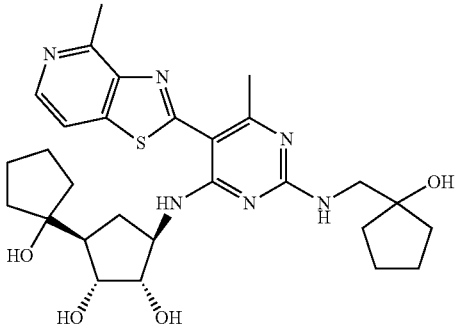
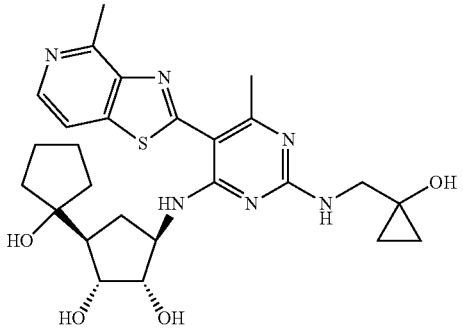
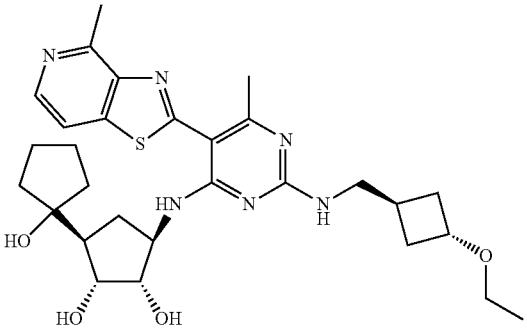
Compd #	Structure	EC90 (μM)	LC-MS or MS
5109		B	537.7
5110		A	555.6
5111		A	527.6
5112		A	569.7

TABLE VI-continued

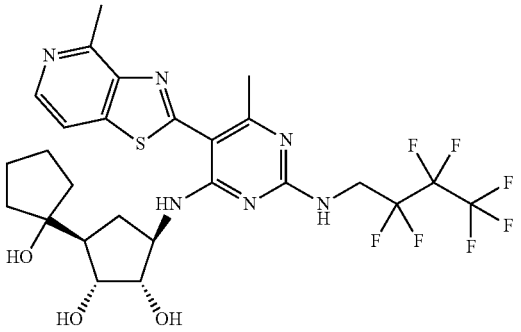
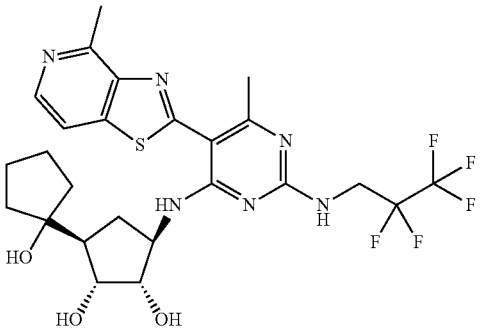
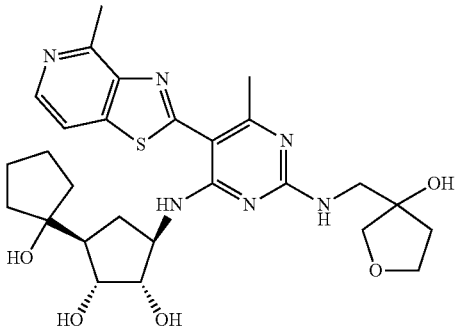
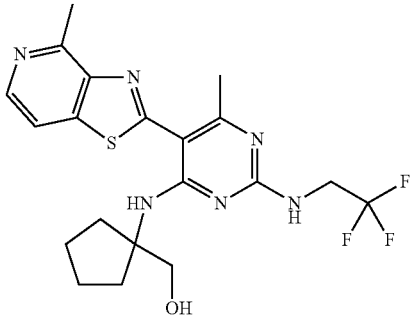
Compd #	Structure	EC90 (μM)	LC-MS or MS
5113		C	639.7
5114		A	589.7
5115		A	557.7
5116		A	453.7

TABLE VI-continued

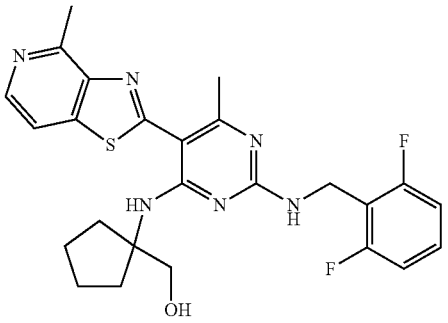
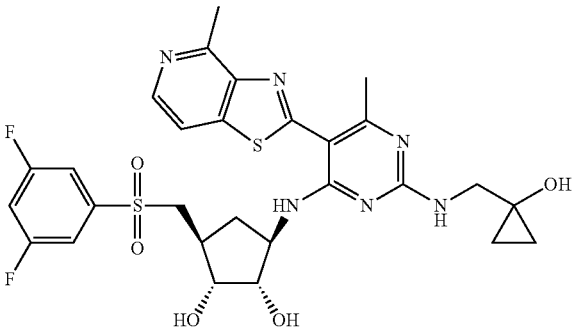
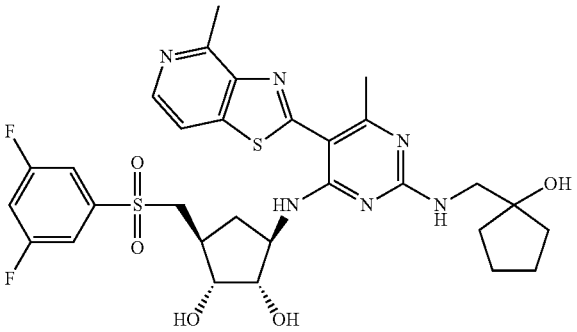
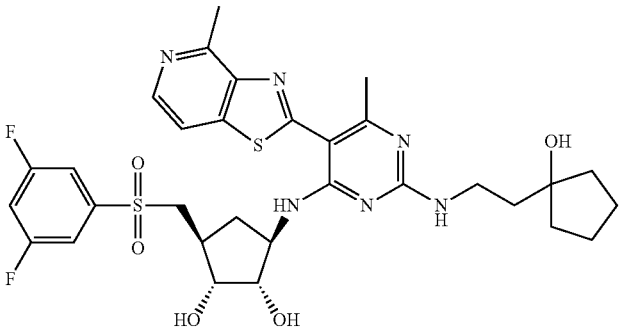
Compd #	Structure	EC90 (μM)	LC-MS or MS
5117		A	497.7
5118		A	633.7
5119		A	661.7
5120		A	675.7

TABLE VI-continued

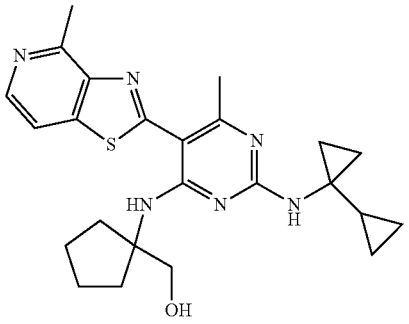
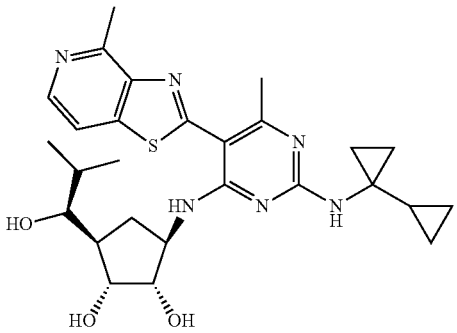
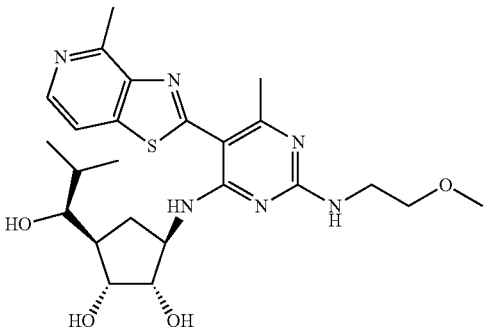
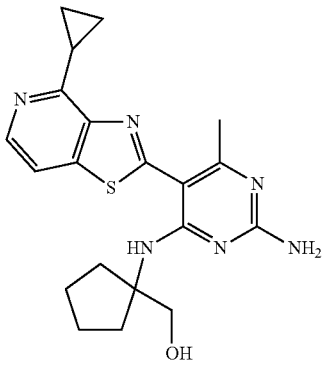
Compd #	Structure	EC90 (μM)	LC-MS or MS
5121		A	451.7
5122		A	525.7
5123		A	503.7
5124		A	397.7

TABLE VI-continued

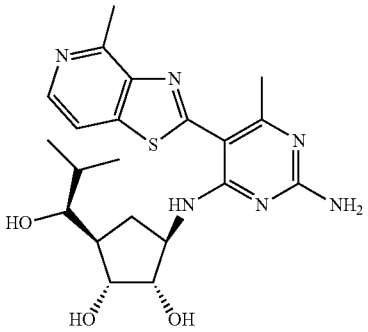
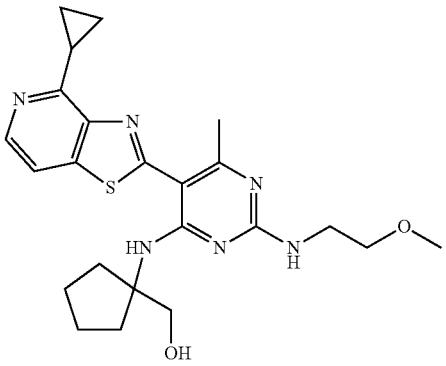
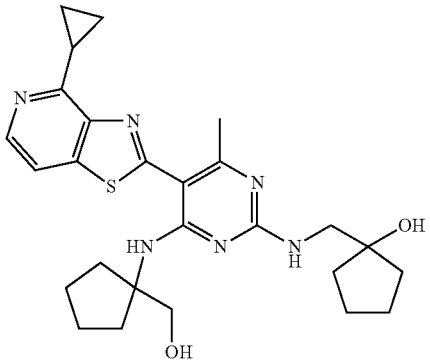
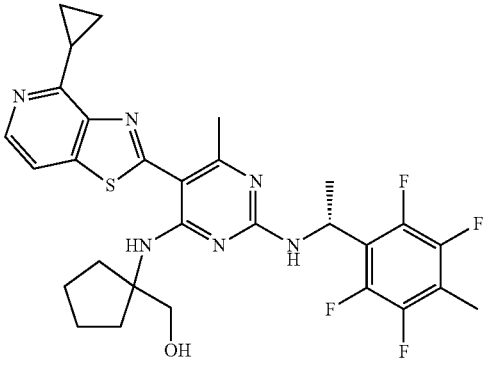
Compd #	Structure	EC90 (μM)	LC-MS or MS
5125		A	445.7
5126		A	455.7
5127		A	495.7
5128		>1.0	587.7

TABLE VI-continued

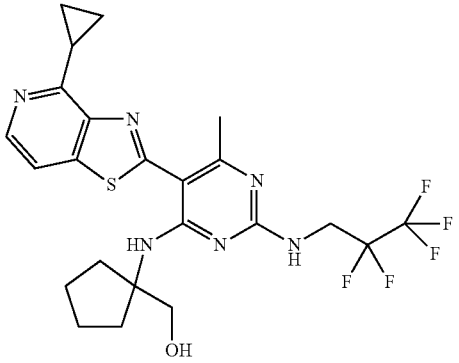
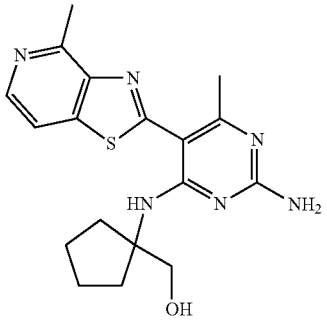
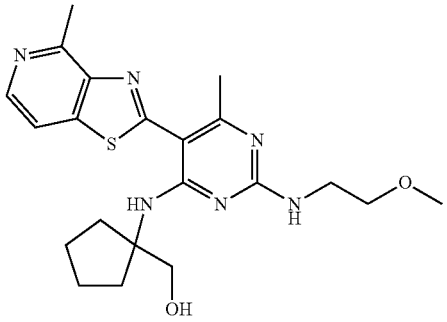
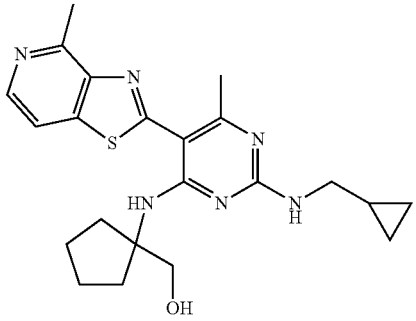
Compd #	Structure	EC90 (μM)	LC-MS or MS
5129		A	529.7
5130		A	371.7
5131		A	429.7
5132		A	425.7

TABLE VI-continued

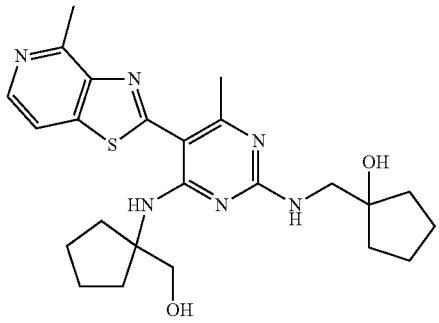
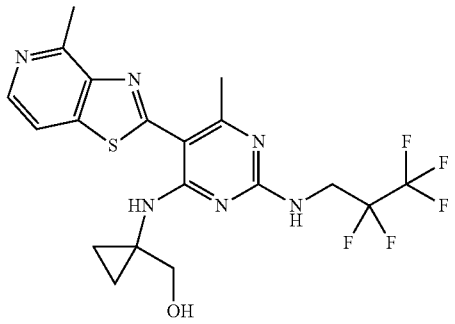
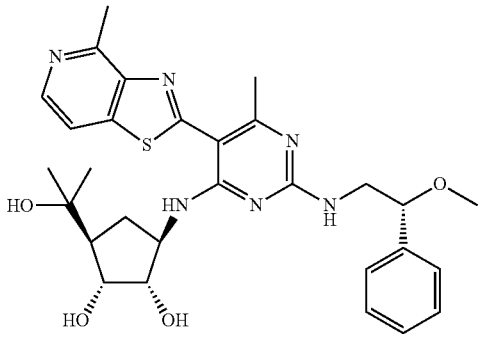
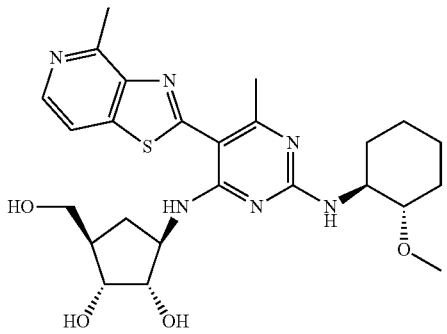
Compd #	Structure	EC90 (μM)	LC-MS or MS
5133		A	469.7
5134		A	475.7
5135		A	565.2
5136		A	515.2

TABLE VI-continued

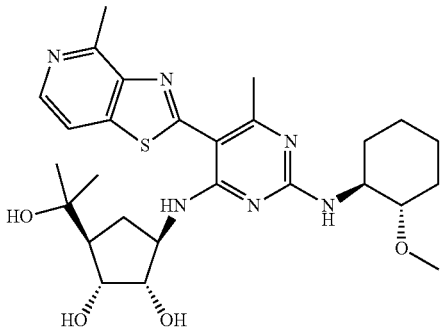
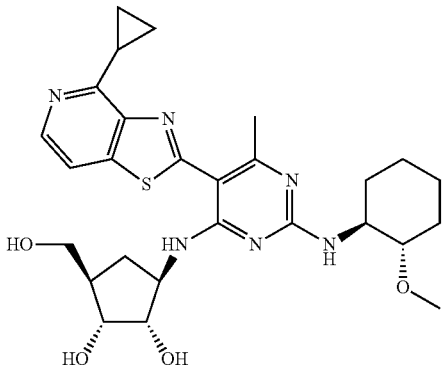
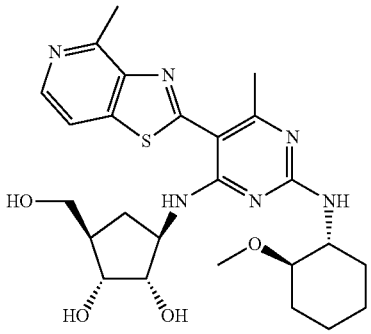
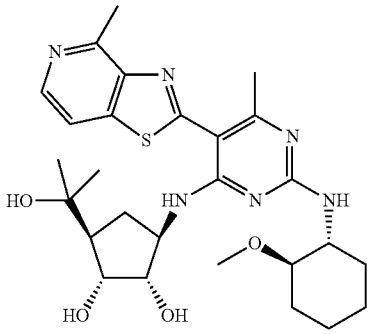
Compd #	Structure	EC90 (μM)	LC-MS or MS
5137		B	543.2
5138		A	541.2
5139		A	515.2
5140		A	543.2

TABLE VI-continued

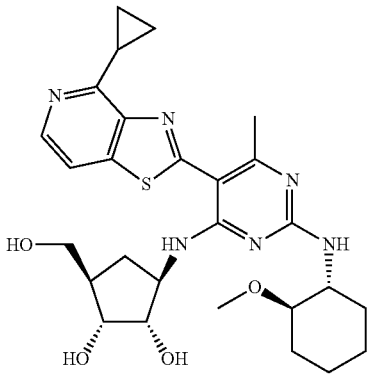
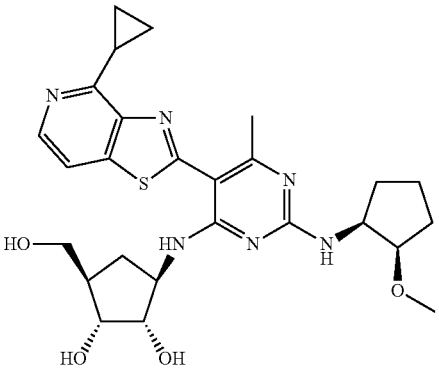
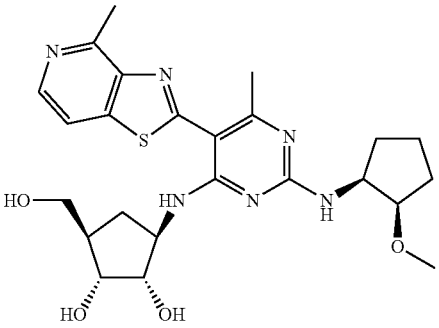
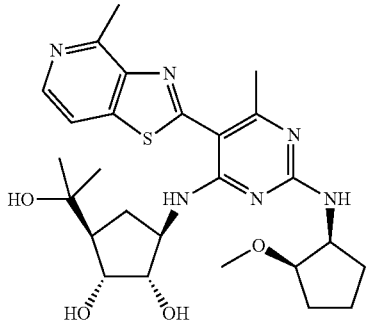
Compd #	Structure	EC90 (μM)	LC-MS or MS
5141		A	541.2
5142		A	527.2
5143		A	501.2
5144		B	529.2

TABLE VI-continued

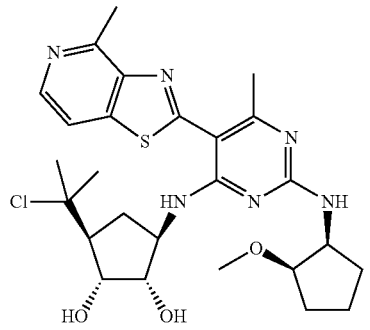
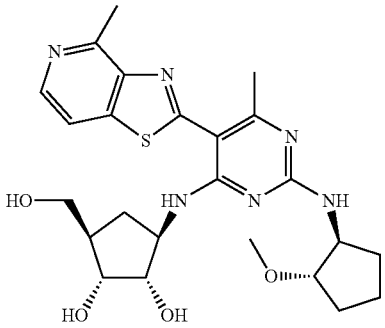
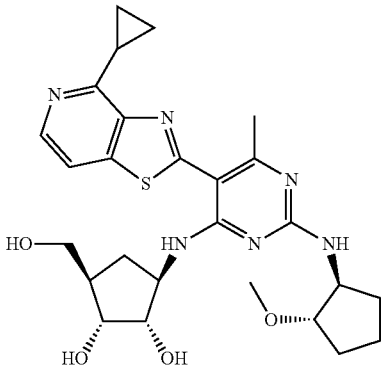
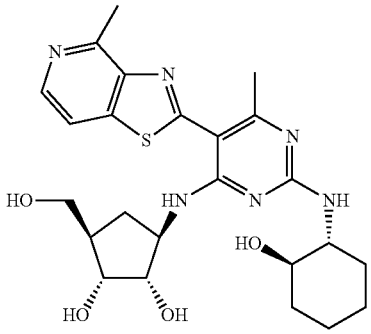
Compd #	Structure	EC90 (μM)	LC-MS or MS
5145		A	547.2
5146		A	501.2
5147		A	527.2
5148		A	501.0

TABLE VI-continued

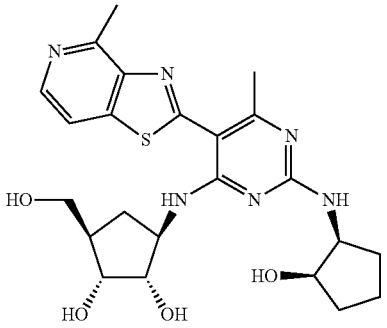
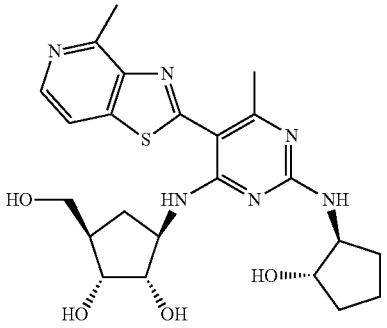
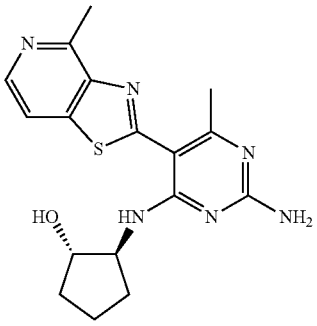
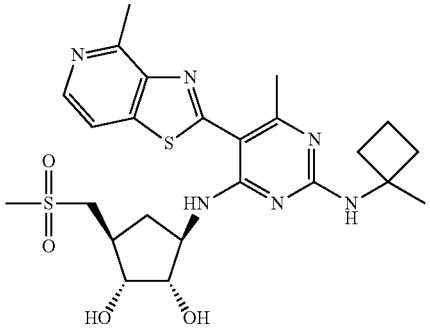
Compd #	Structure	EC90 (μM)	LC-MS or MS
5149		A	487.0
5150		A	487.0
5151		A	357.0
5152		A	533.0

TABLE VI-continued

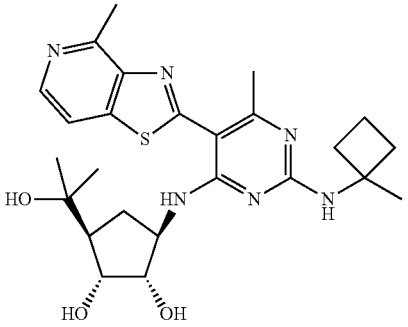
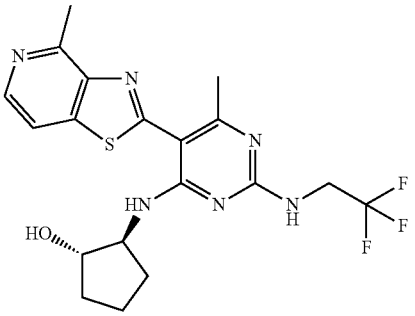
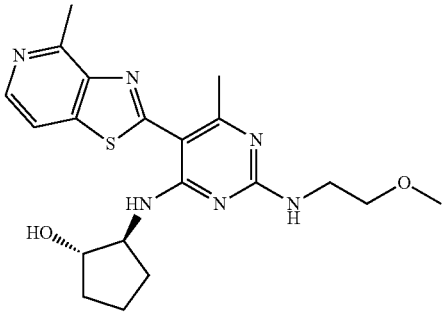
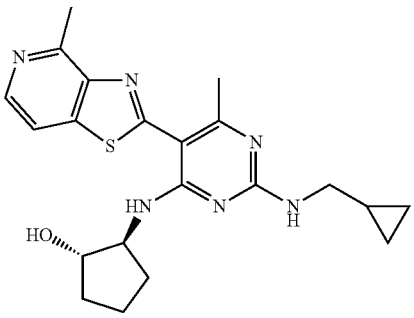
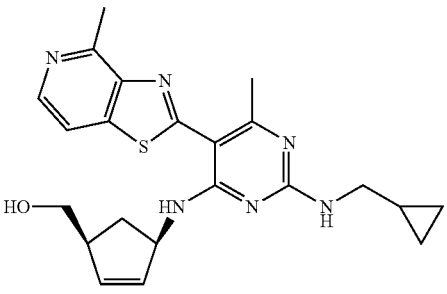
Compd #	Structure	EC90 (μM)	LC-MS or MS
5153		A	499.0
5154		A	439.0
5155		A	415.0
5156		A	411.0
5157		A	423.2

TABLE VI-continued

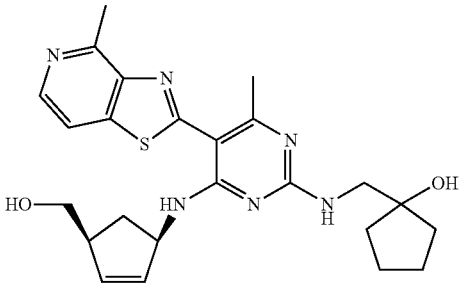
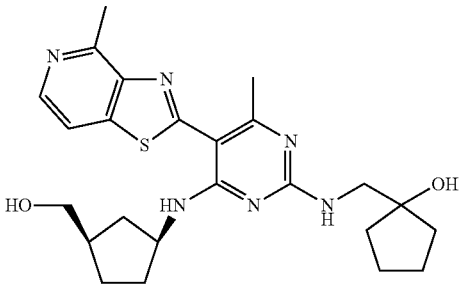
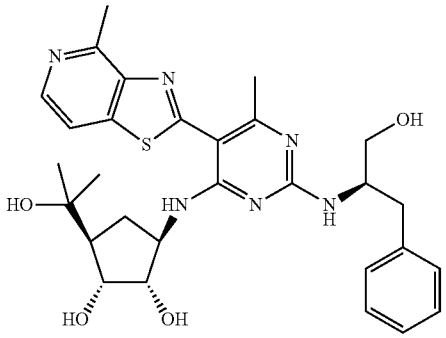
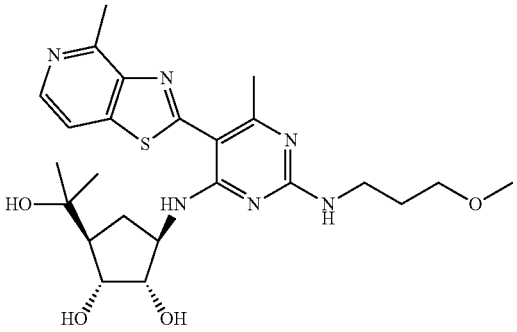
Compd #	Structure	EC90 (μM)	LC-MS or MS
5158		A	467.3
5159		A	469.3
5160		B	565.3
5161		A	503.3

TABLE VI-continued

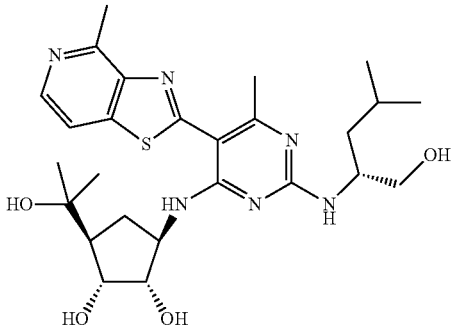
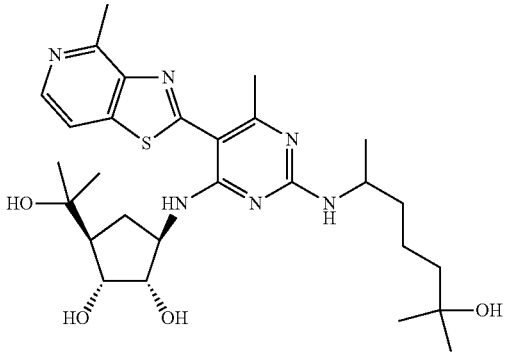
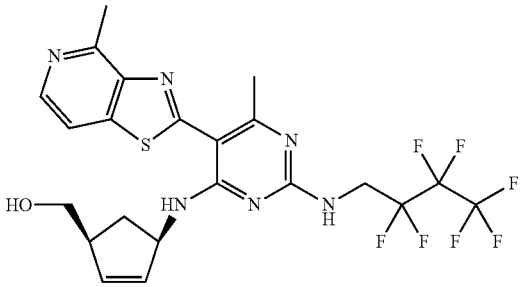
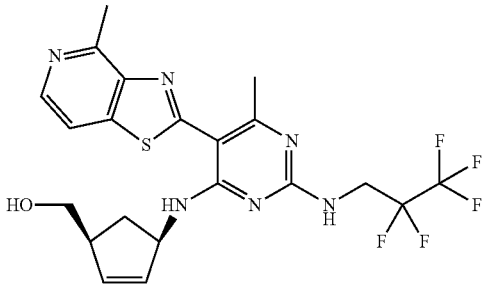
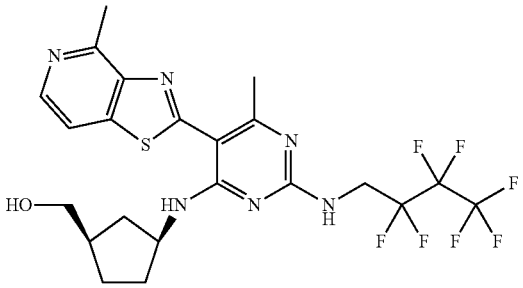
Compd #	Structure	EC90 (μM)	LC-MS or MS
5162		A	531.3
5163		A	559.3
5164		A	551.3
5165		A	501.3
5166		A	553.3

TABLE VI-continued

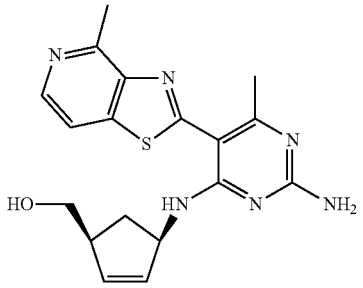
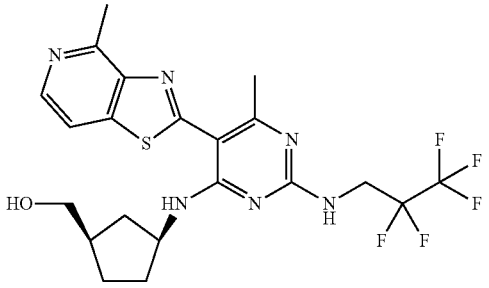
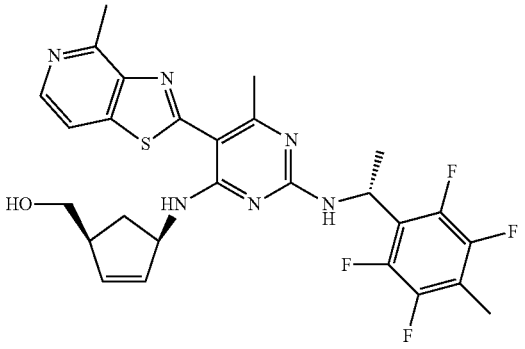
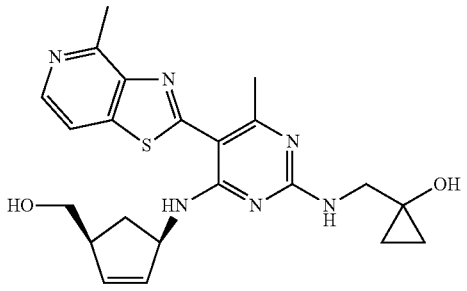
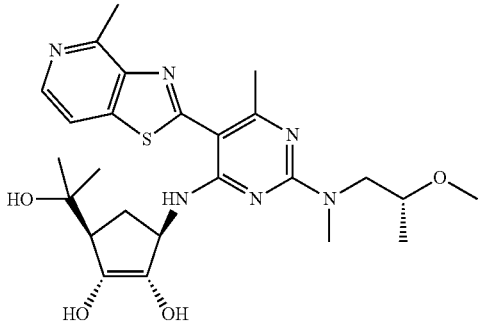
Compd #	Structure	EC90 (μM)	LC-MS or MS
5167		A	369.2
5168		A	503.3
5169		A	559.3
5170		A	439.2
5171		>1.0	517.4

TABLE VI-continued

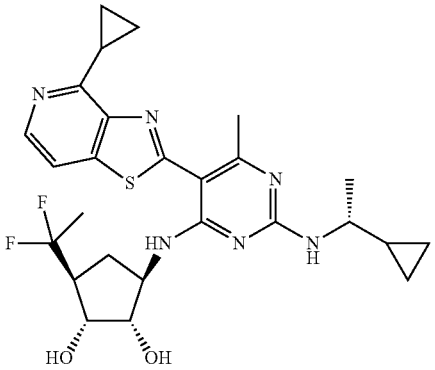
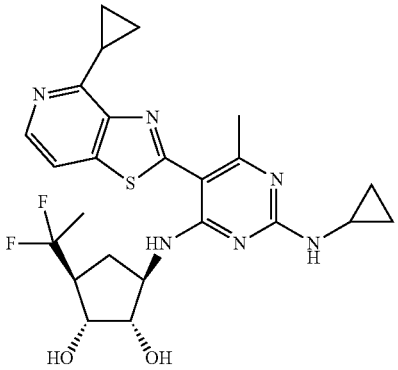
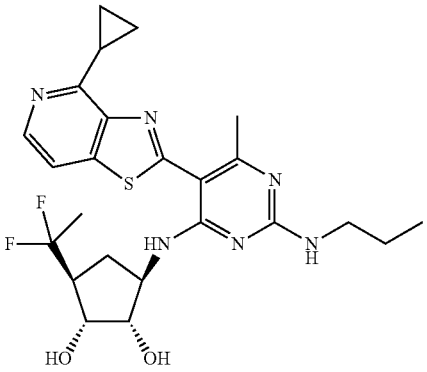
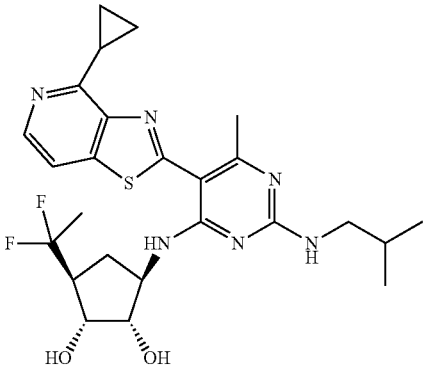
Compd #	Structure	EC90 (μM)	LC-MS or MS
5172		A	531.3
5173		A	503.3
5174		A	505.4
5175		A	519.3

TABLE VI-continued

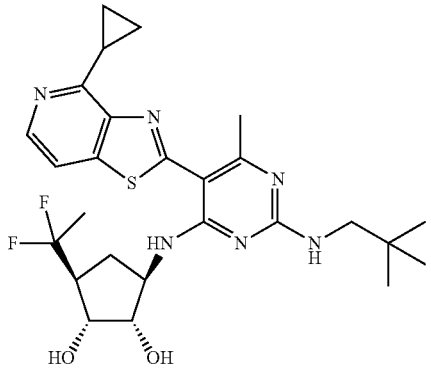
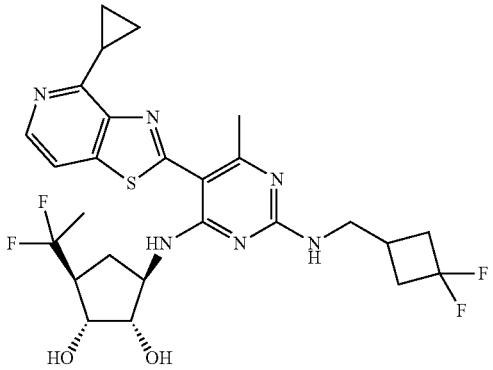
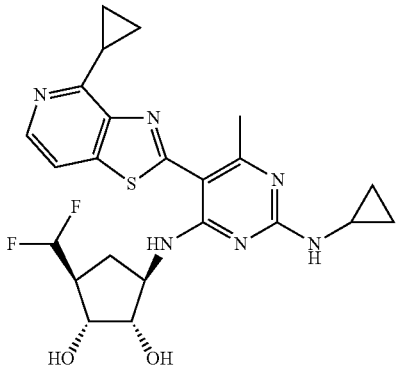
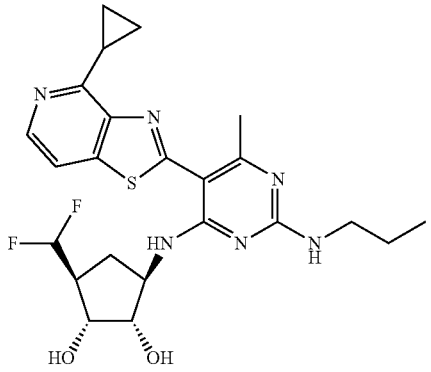
Compd #	Structure	EC90 (μM)	LC-MS or MS
5176		A	533.3
5177		A	567.3
5178		A	489.3
5179		A	491.3

TABLE VI-continued

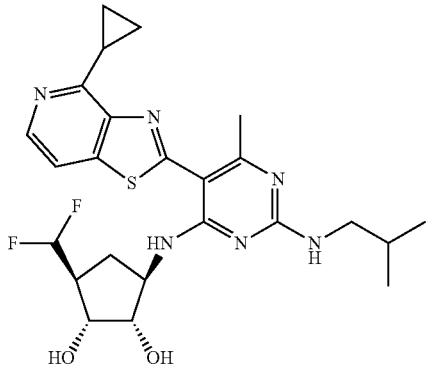
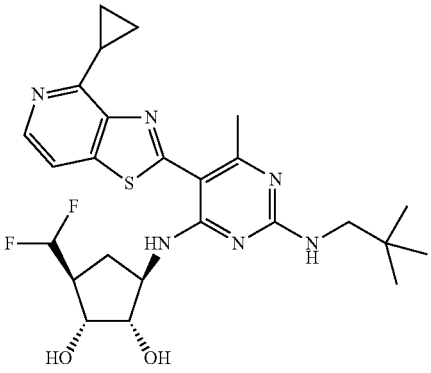
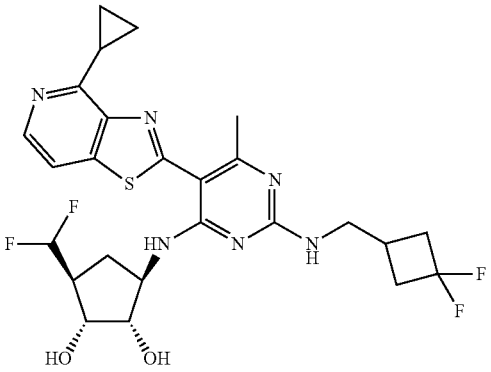
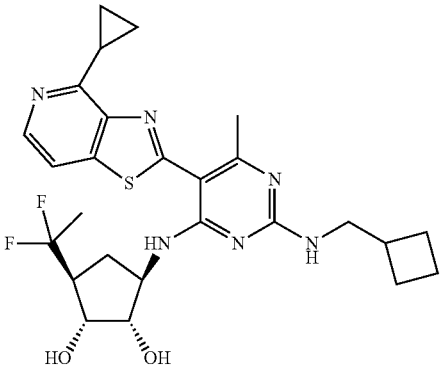
Compd #	Structure	EC90 (μM)	LC-MS or MS
5180		A	505.3
5181		A	519.3
5182		A	553.3
5183		A	531.3

TABLE VI-continued

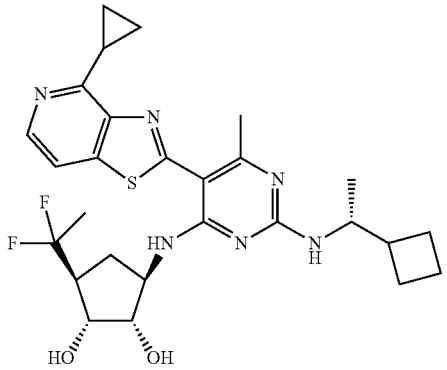
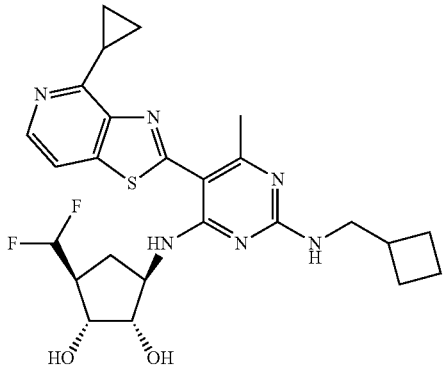
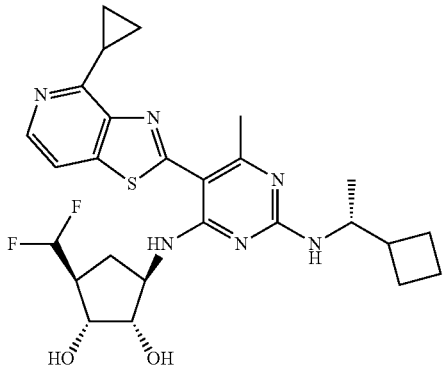
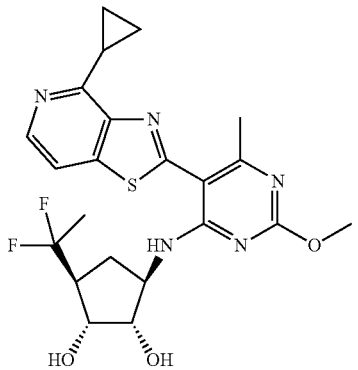
Compd #	Structure	EC90 (μM)	LC-MS or MS
5184		A	545.3
5185		A	517.3
5186		A	531.3
5187		C	478.3

TABLE VI-continued

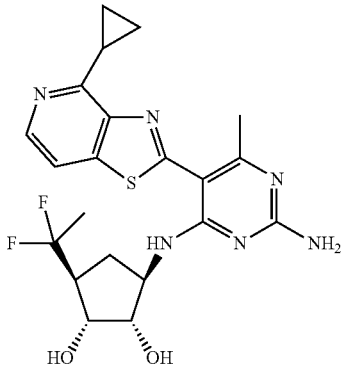
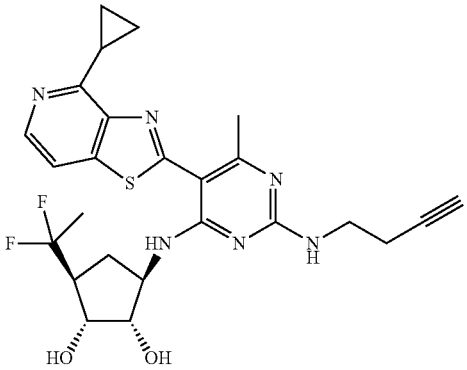
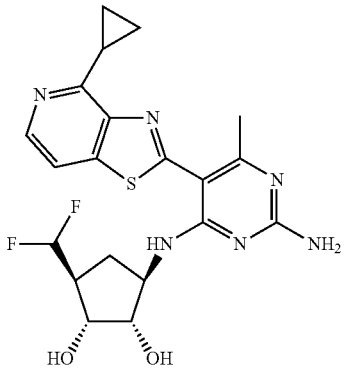
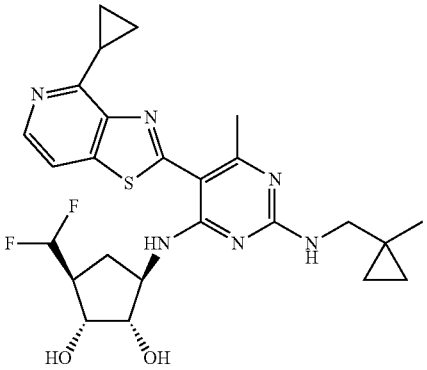
Compd #	Structure	EC90 (μM)	LC-MS or MS
5188		A	463.3
5189		A	515.3
5190		A	449.2
5191		A	517.3

TABLE VI-continued

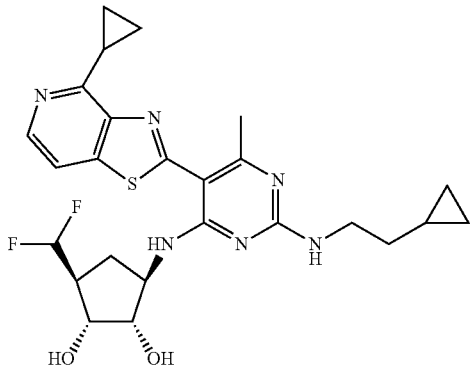
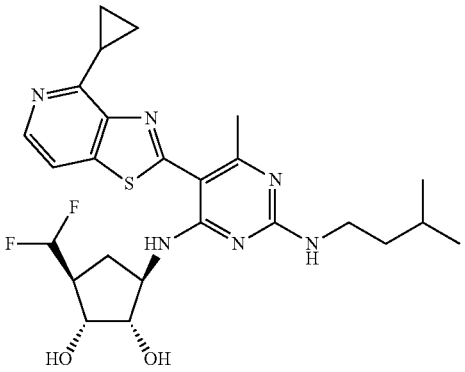
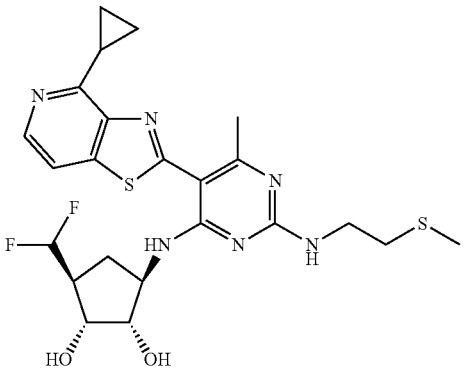
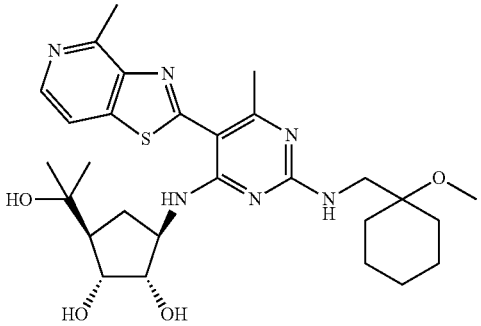
Compd #	Structure	EC90 (μM)	LC-MS or MS
5192		A	517.3
5193		A	519.4
5194		A	523.3
5195		A	557.5

TABLE VI-continued

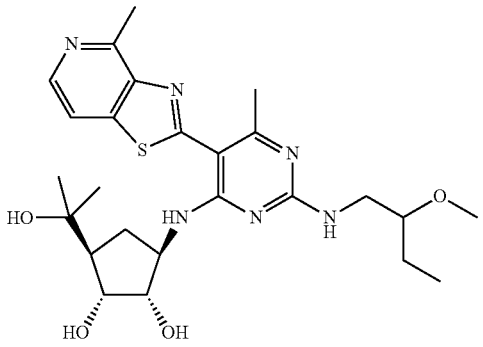
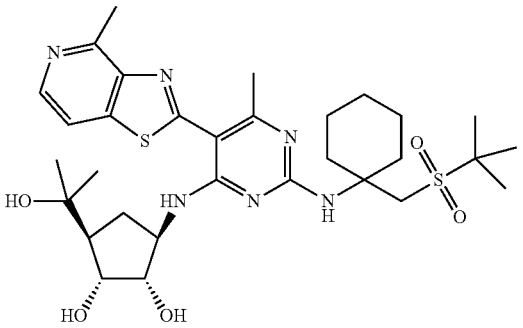
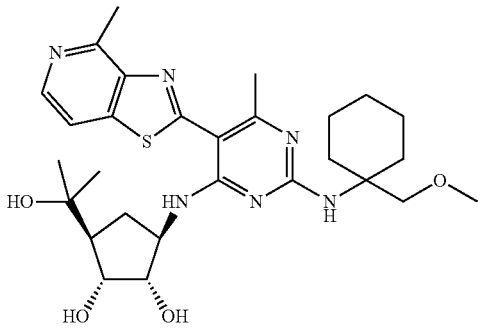
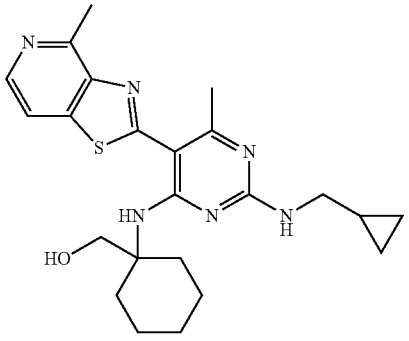
Compd #	Structure	EC90 (μM)	LC-MS or MS
5196		A	517.4
5197		>1.0	647.6
5198		>1.0	557.5
5199		A	439.4

TABLE VI-continued

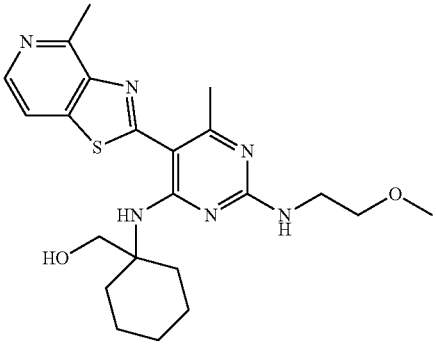
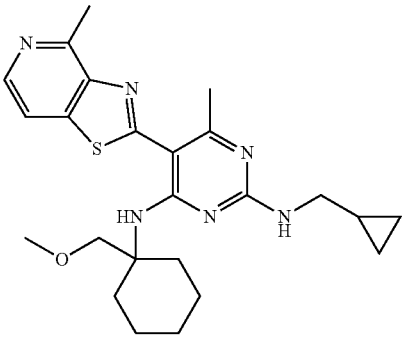
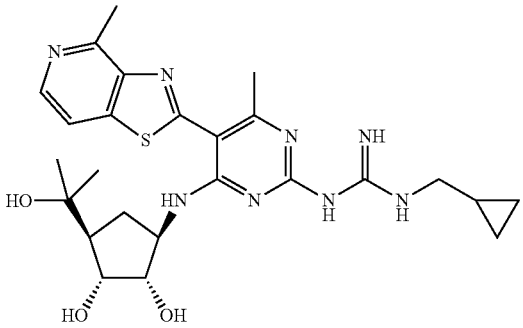
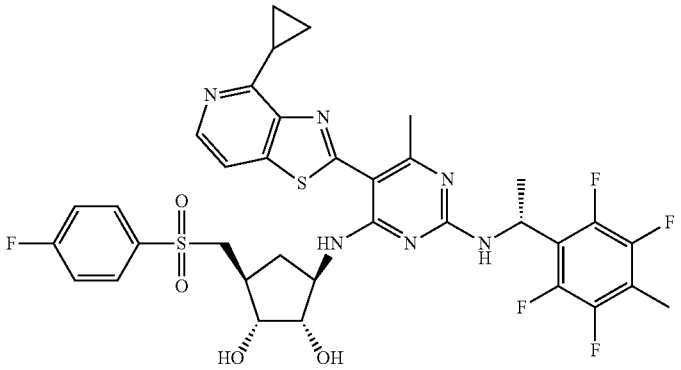
Compd #	Structure	EC90 (μM)	LC-MS or MS
5200		A	443.3
5201		A	453.4
5202		D	527.3
5203		B	761.2

TABLE VI-continued

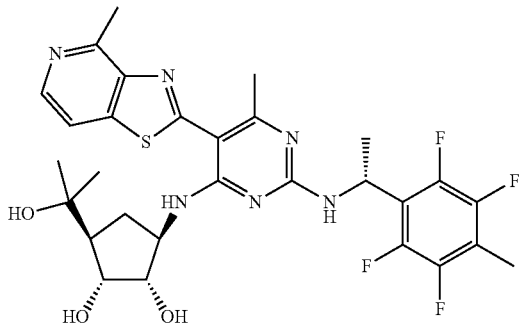
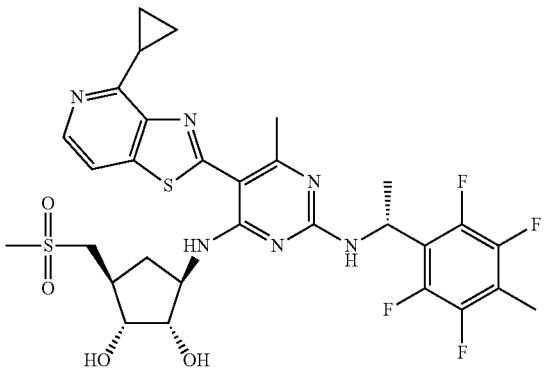
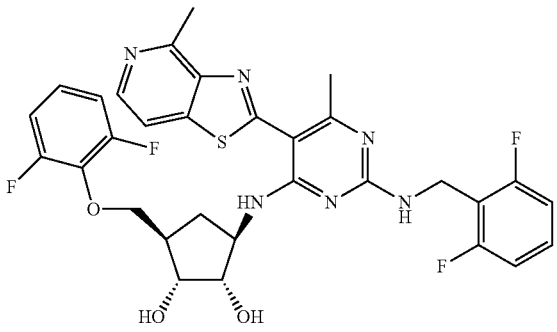
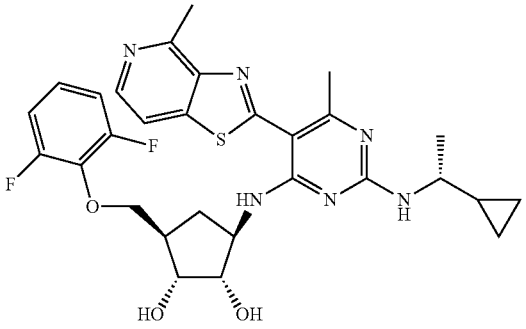
Compd #	Structure	EC90 (μM)	LC-MS or MS
5204		A	621.2
5205		A	681.0
5206		A	641.4
5207		A	583.2

TABLE VI-continued

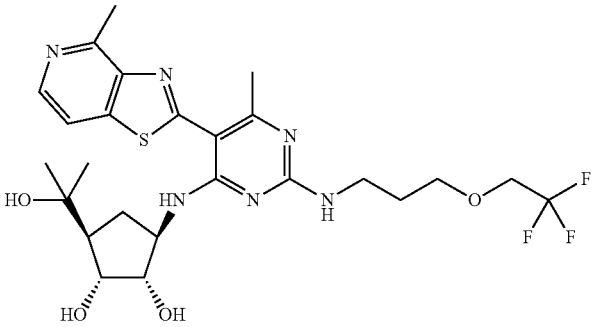
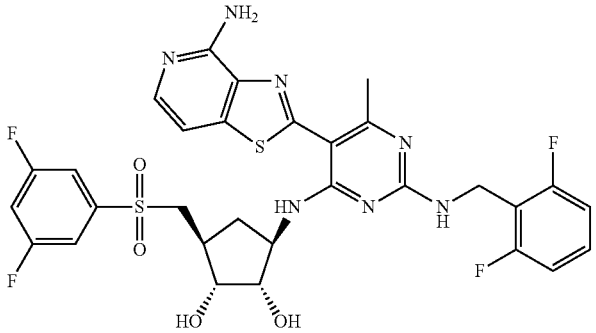
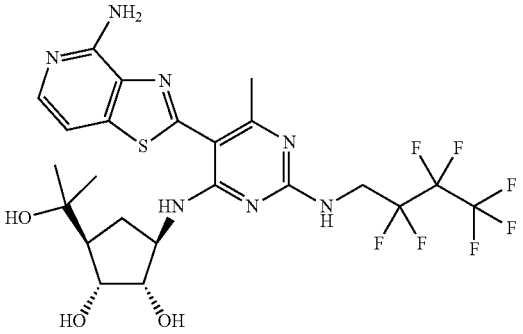
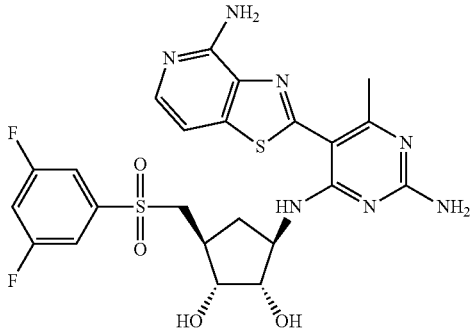
Compd #	Structure	EC90 (μM)	LC-MS or MS
5208		A	571.2
5209		A	690.1
5210		A	613.3
5211		A	564.1

TABLE VI-continued

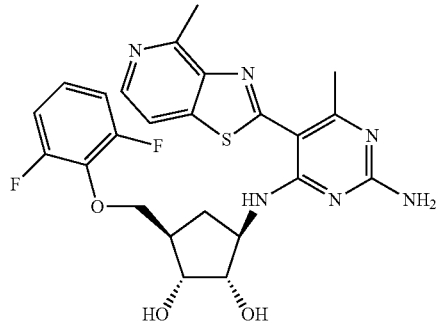
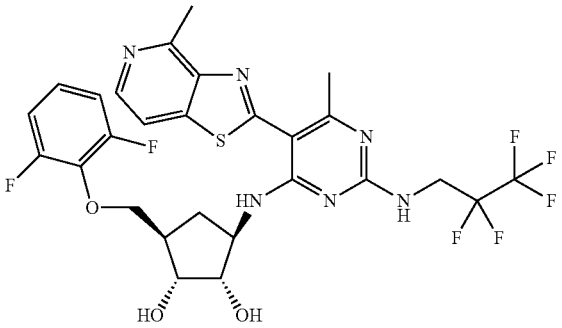
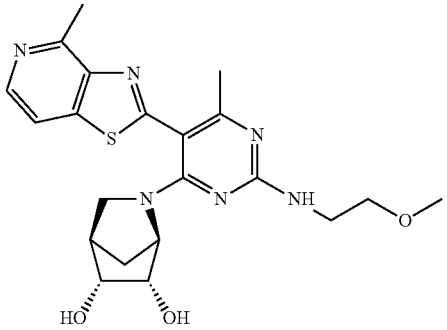
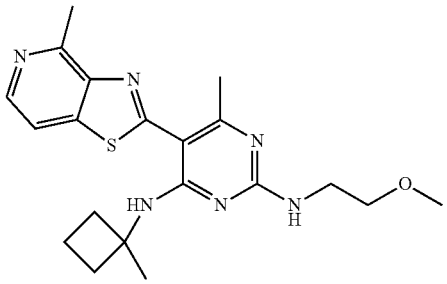
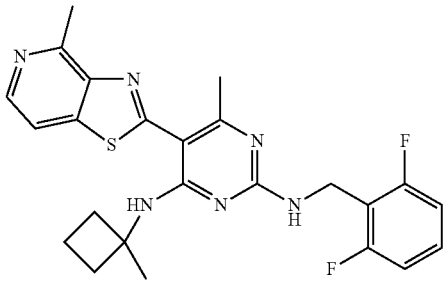
Compd #	Structure	EC90 (μM)	LC-MS or MS
5212		A	515.2
5213		A	647.2
5214		>1.0	443.2
5215		A	399.2
5216		A	467.2

TABLE VI-continued

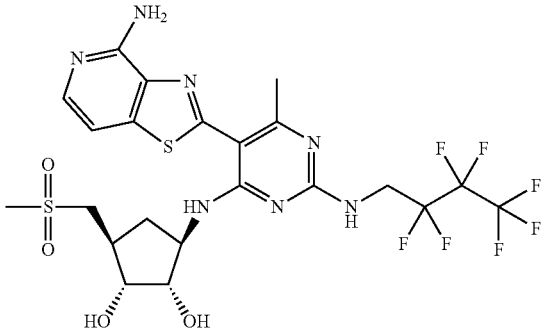
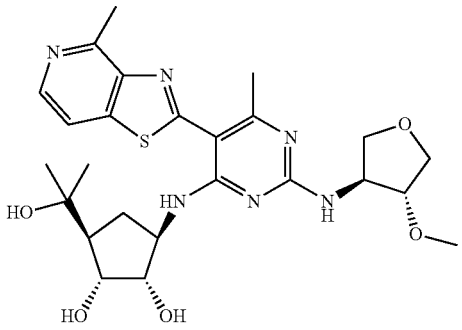
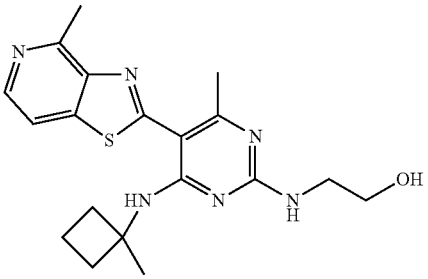
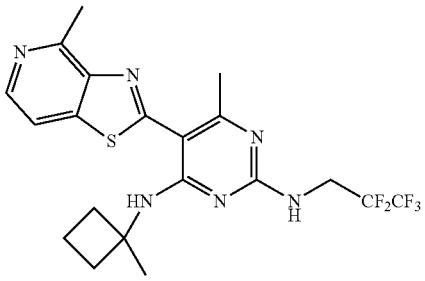
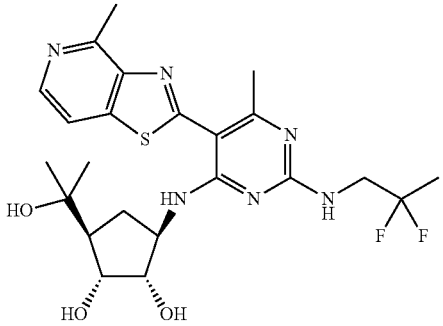
Compd #	Structure	EC90 (μM)	LC-MS or MS
5217		A	673.1
5218		A	531.2
5219		A	385.2
5220		B	473.2
5221		A	509.3

TABLE VI-continued

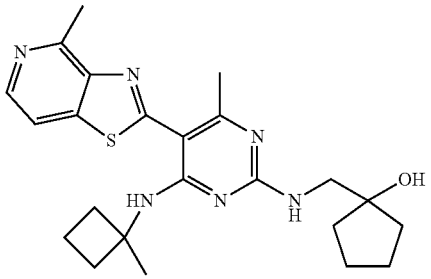
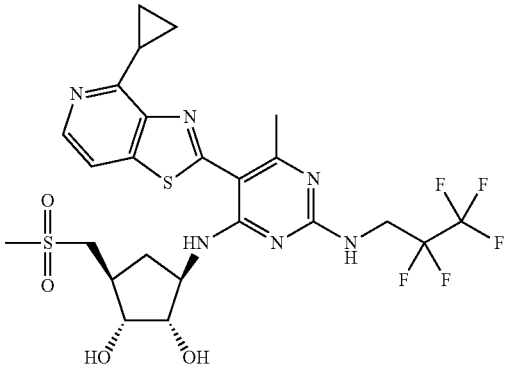
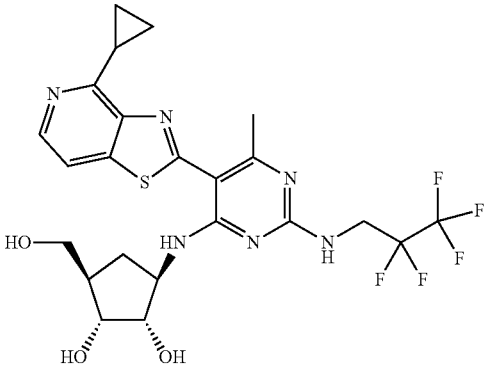
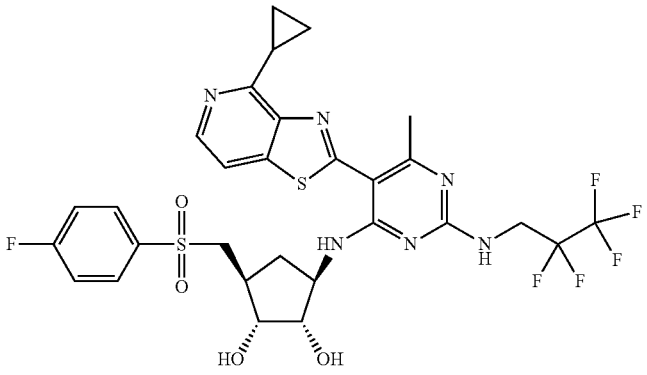
Compd #	Structure	EC90 (μM)	LC-MS or MS
5222		A	439.2
5223		A	623.2
5224		A	561.2
5225		A	703.1

TABLE VI-continued

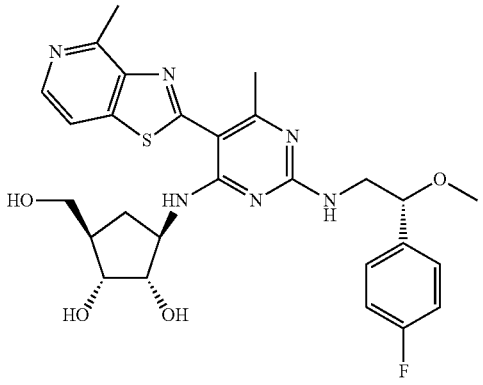
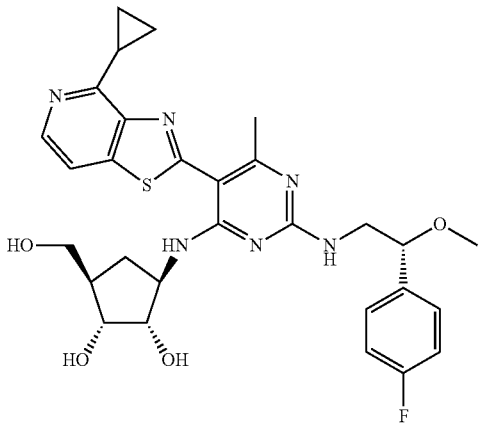
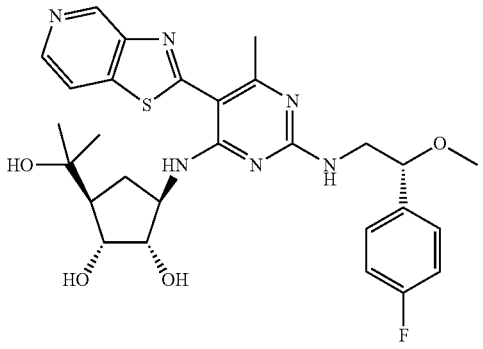
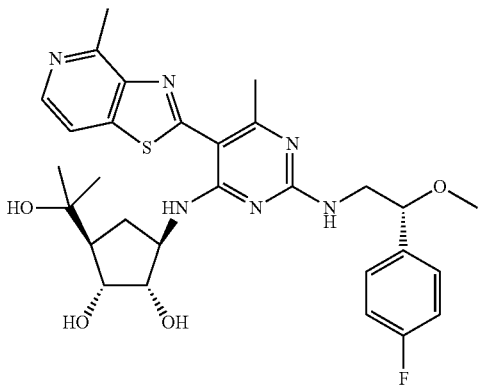
Compd #	Structure	EC90 (μM)	LC-MS or MS
5226		A	555.2
5227		A	581.2
5228		A	569.2
5229		A	583.2

TABLE VI-continued

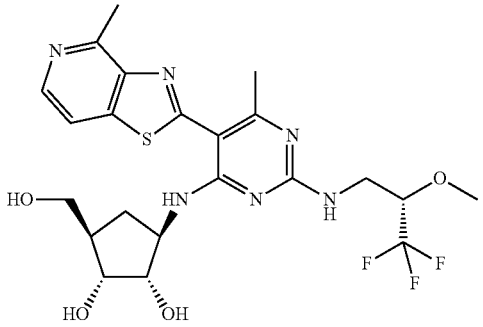
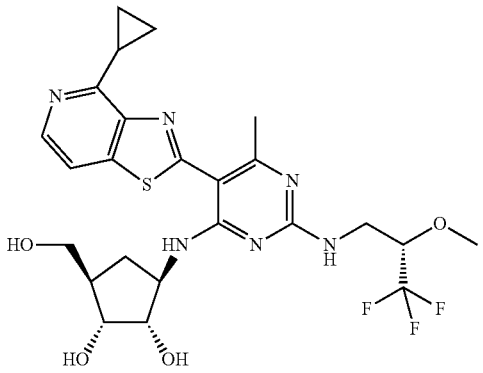
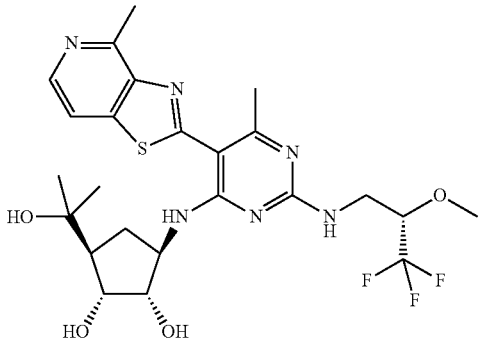
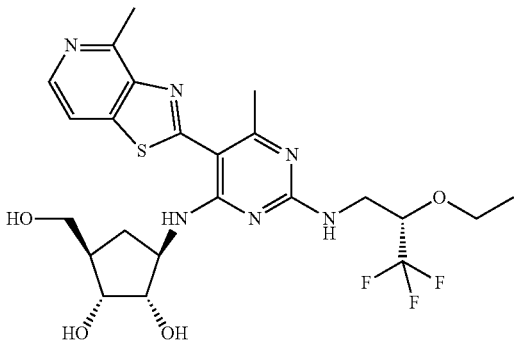
Compd #	Structure	EC90 (μM)	LC-MS or MS
5230		A	529.2
5231		A	555.2
5232		A	557.2
5233		A	543.0

TABLE VI-continued

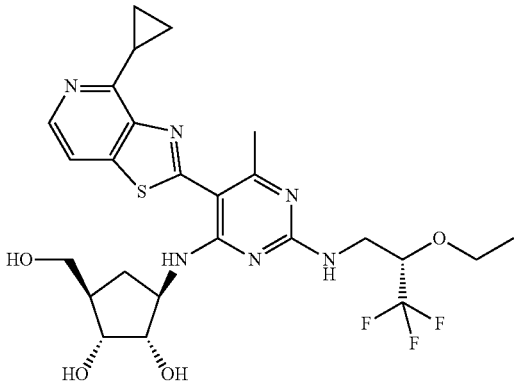
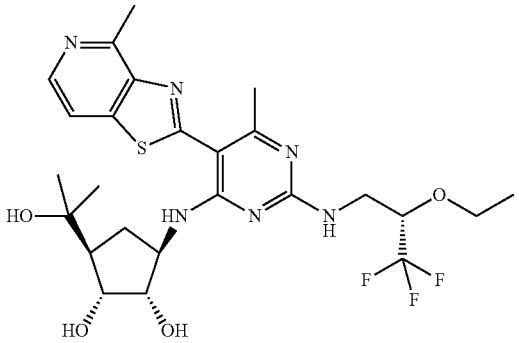
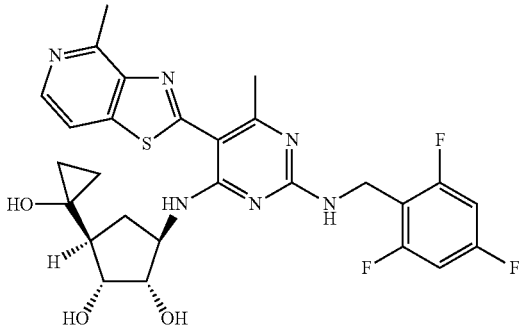
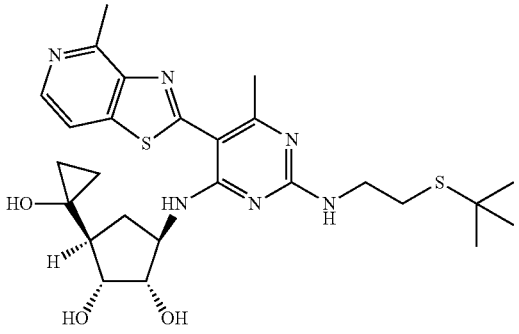
Compd #	Structure	EC90 (μM)	LC-MS or MS
5234		A	569.0
5235		A	571.0
5236		A	573.2
5237		A	545.2

TABLE VI-continued

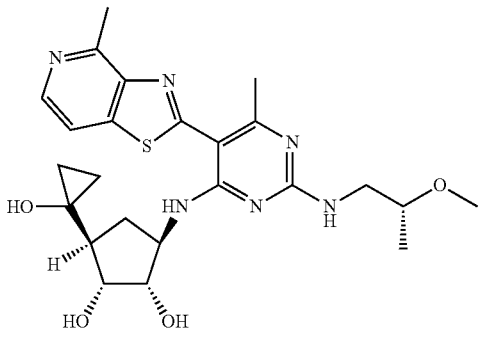
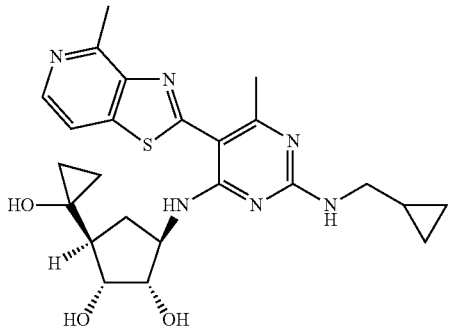
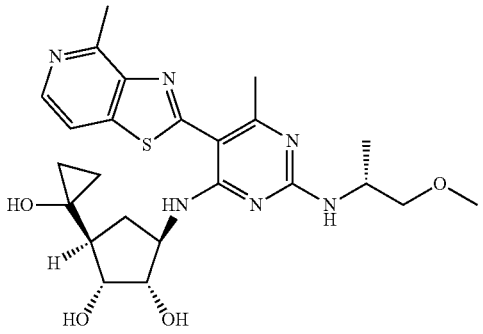
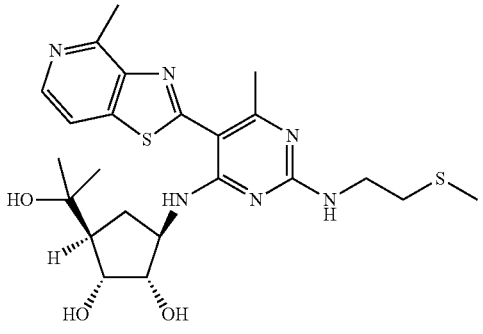
Compd #	Structure	EC90 (μM)	LC-MS or MS
5238		A	501.2
5239		A	483.2
5240		A	501.2
5241		A	505.2

TABLE VI-continued

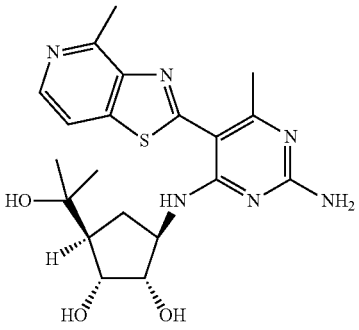
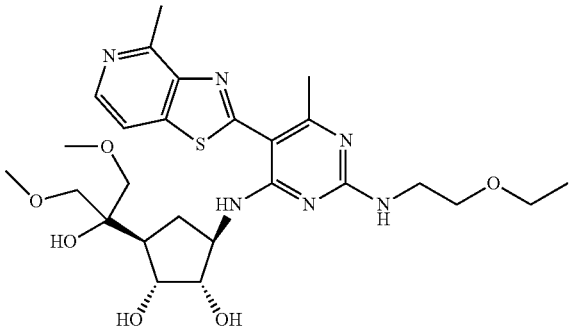
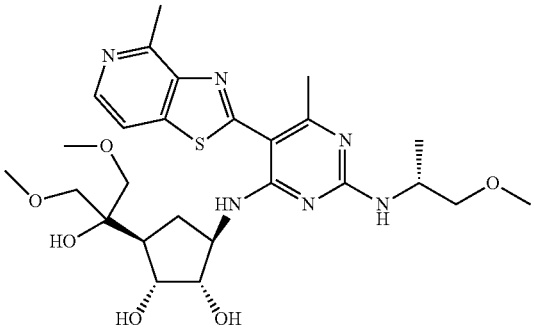
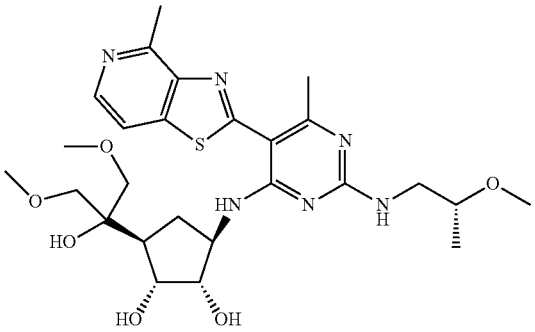
Compd #	Structure	EC90 (μM)	LC-MS or MS
5242		A	431.2
5243		A	563.2
5244		A	563.2
5245		A	563.2

TABLE VI-continued

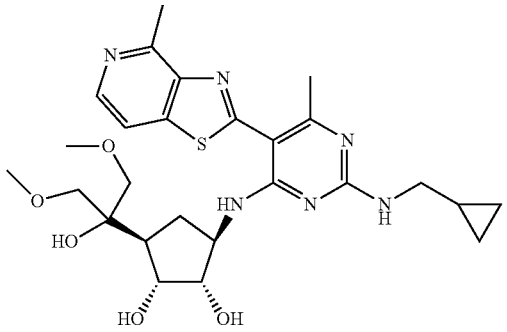
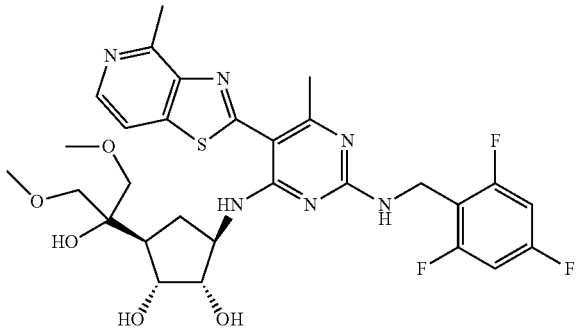
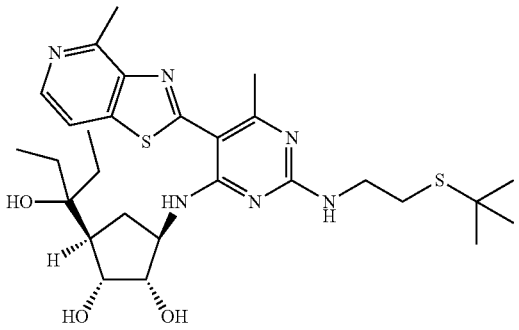
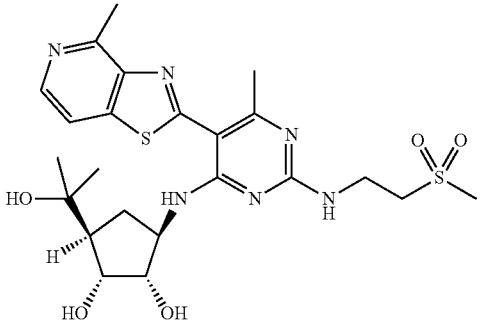
Compd #	Structure	EC90 (μM)	LC-MS or MS
5246		A	545.2
5247		A	635.2
5248		A	575.2
5249		B	537.2

TABLE VI-continued

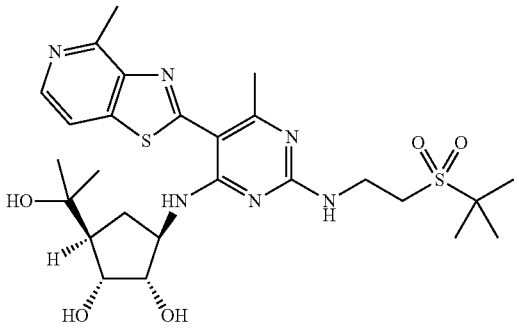
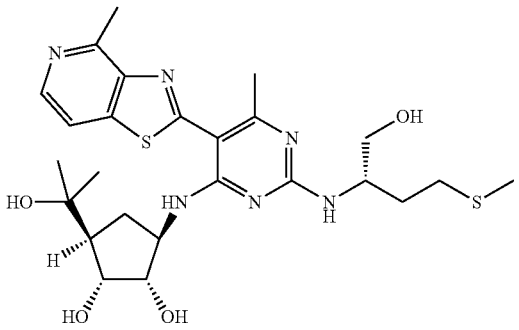
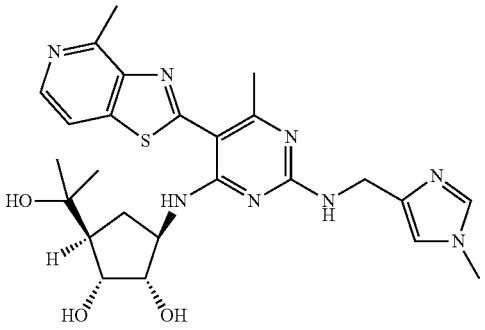
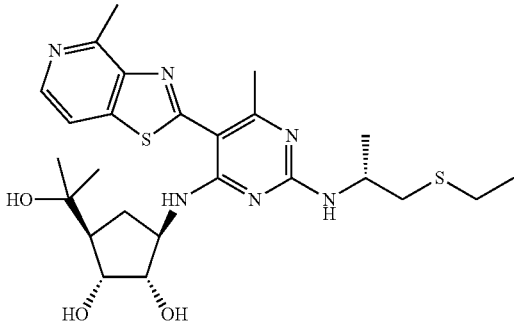
Compd #	Structure	EC90 (μM)	LC-MS or MS
5250		A	579.2
5251		A	549.2
5252		A	525.2
5253		A	533.2

TABLE VI-continued

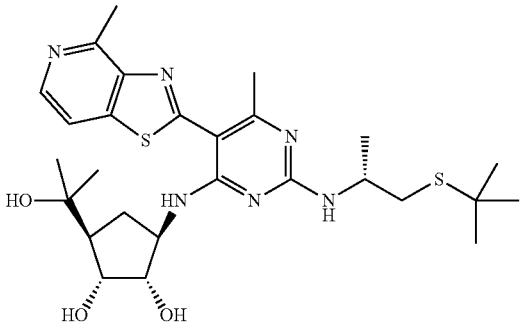
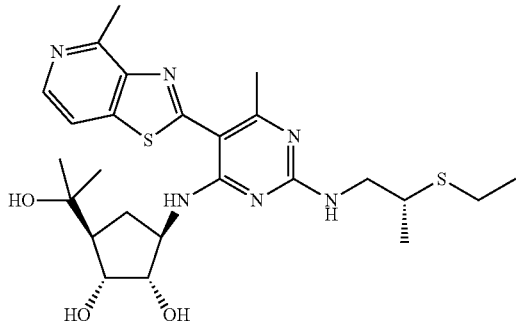
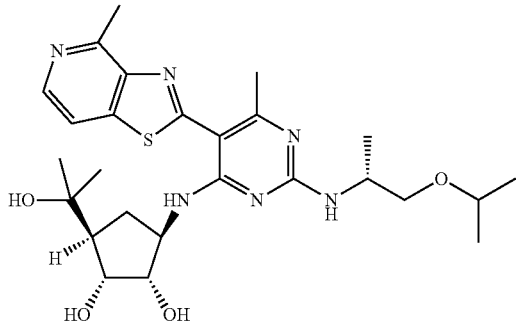
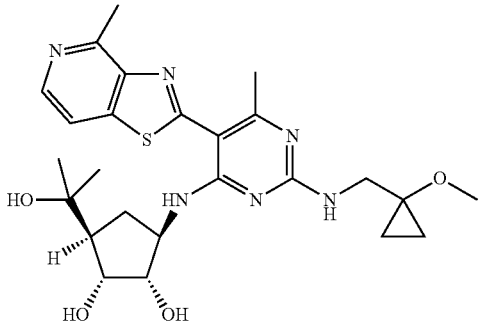
Compd #	Structure	EC90 (μM)	LC-MS or MS
5254		A	561.2
5255		A	533.2
5256		A	531.2
5257		A	515.2

TABLE VI-continued

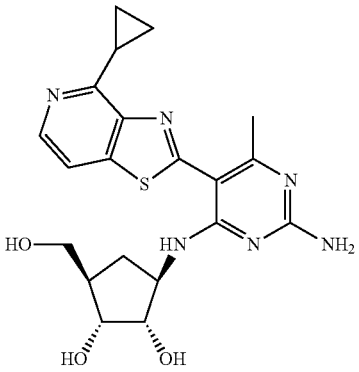
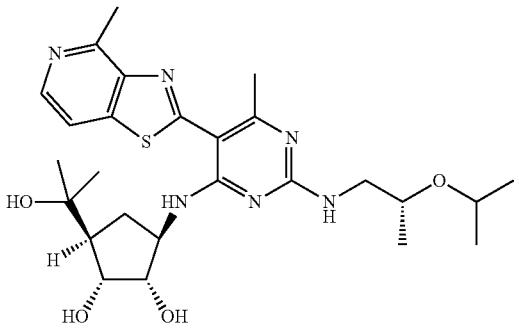
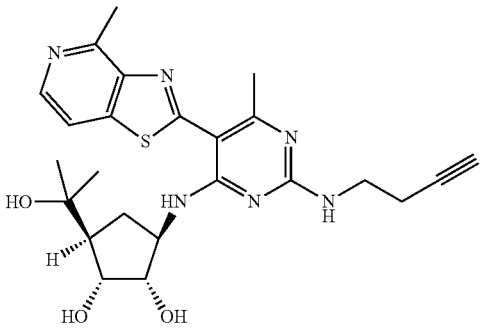
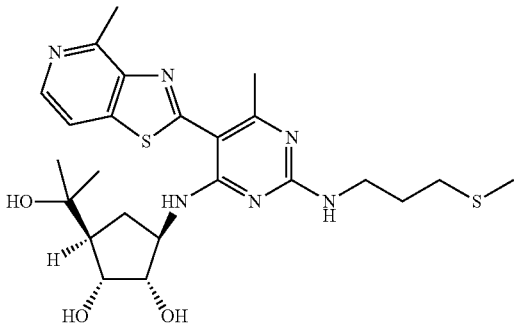
Compd #	Structure	EC90 (μM)	LC-MS or MS
5258		A	429.2
5259		A	531.2
5260		A	483.2
5261		A	519.2

TABLE VI-continued

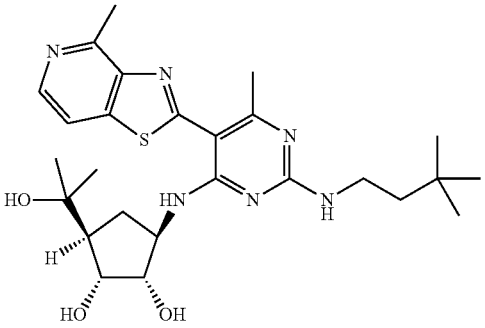
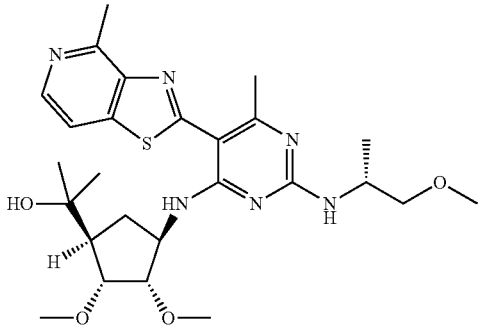
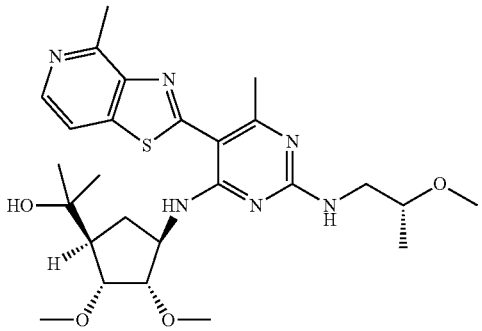
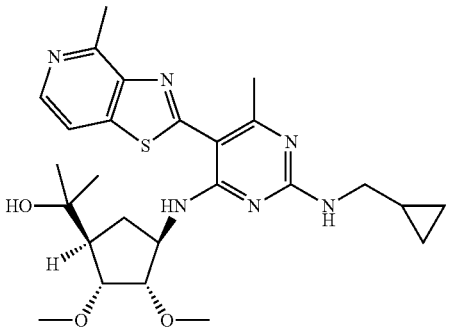
Compd #	Structure	EC90 (μM)	LC-MS or MS
5262		A	515.2
5263		A	531.2
5264		A	531.2
5265		A	513.2

TABLE VI-continued

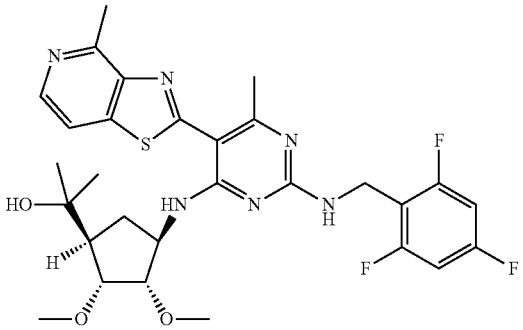
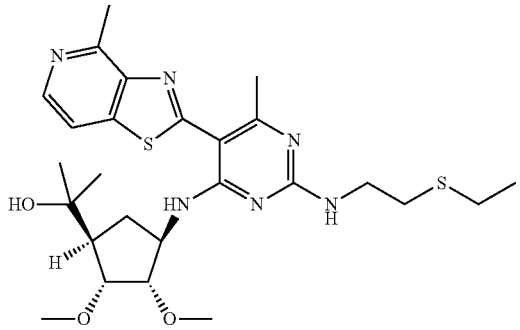
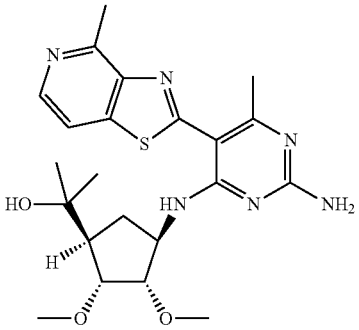
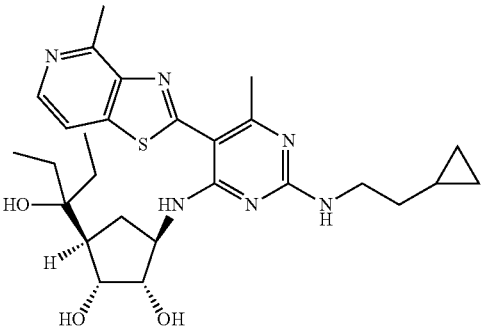
Compd #	Structure	EC90 (μM)	LC-MS or MS
5266		A	603.2
5267		A	547.2
5268		A	459.2
5269		B	527.2

TABLE VI-continued

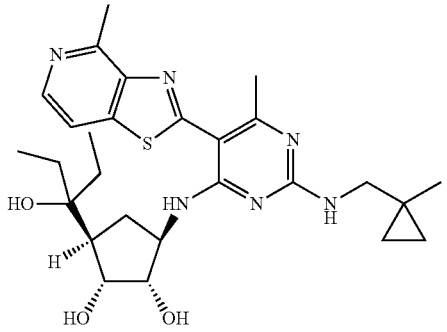
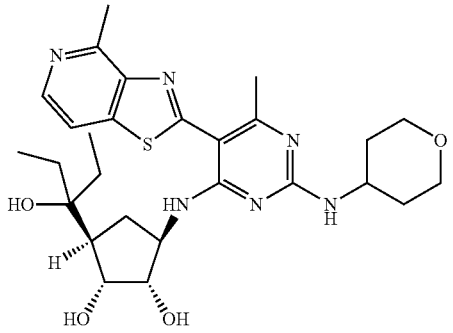
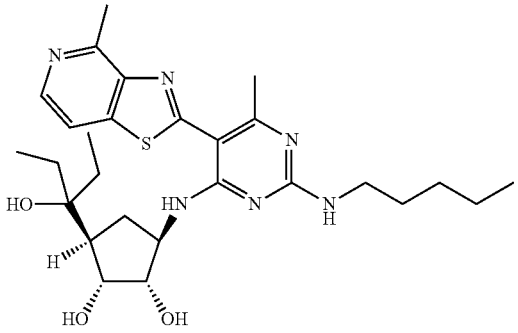
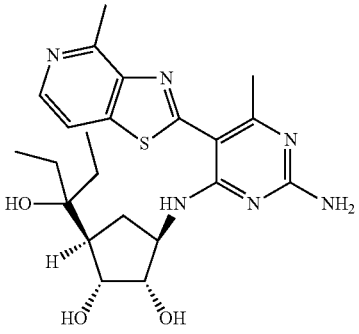
Compd #	Structure	EC90 (μM)	LC-MS or MS
5270		A	527.2
5271		A	543.2
5272		A	529.3
5273		A	459.2

TABLE VI-continued

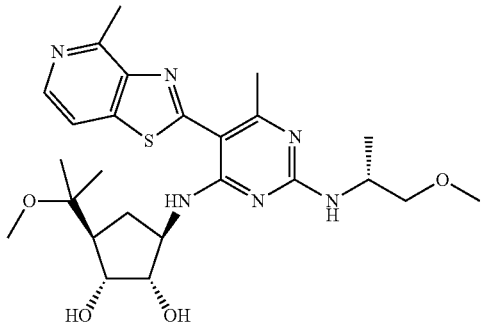
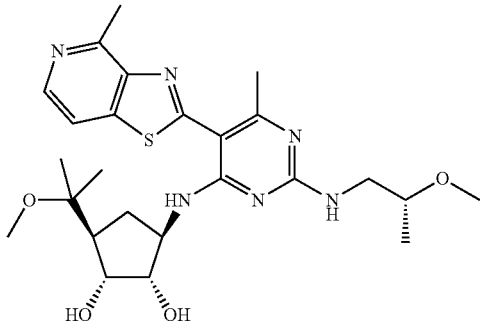
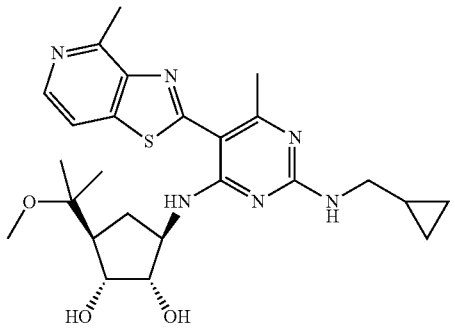
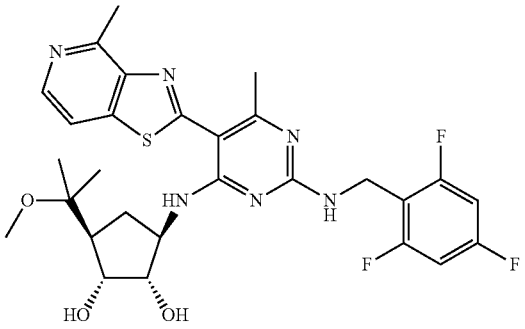
Compd #	Structure	EC90 (μM)	LC-MS or MS
5274		A	517.2
5275		A	517.2
5276		A	499.2
5277		A	589.2

TABLE VI-continued

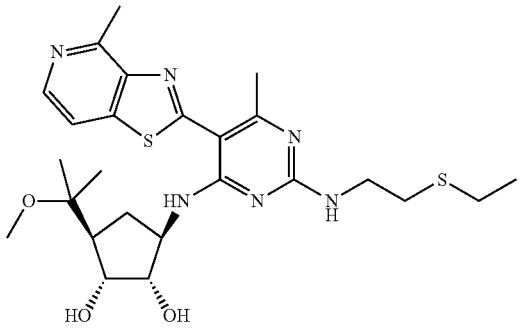
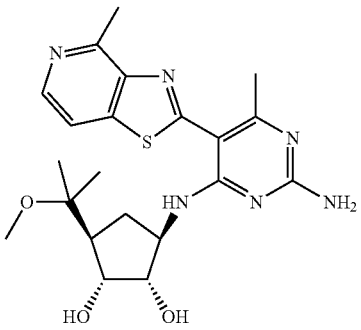
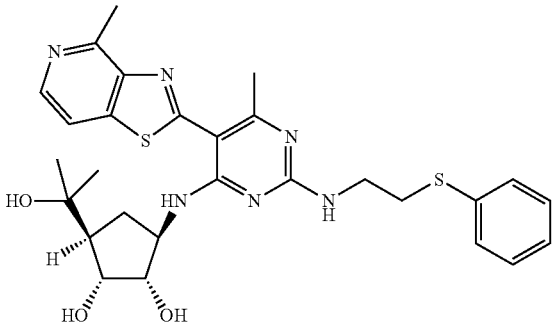
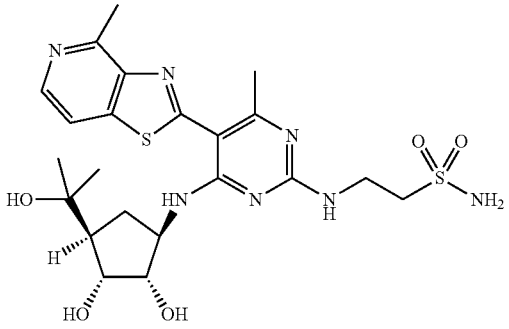
Compd #	Structure	EC90 (μM)	LC-MS or MS
5278		A	533.2
5279		A	445.2
5280		A	567.2
5281		B	538.2

TABLE VI-continued

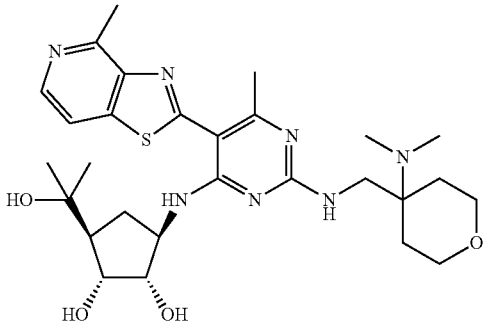
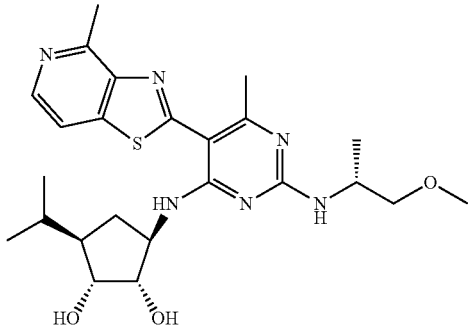
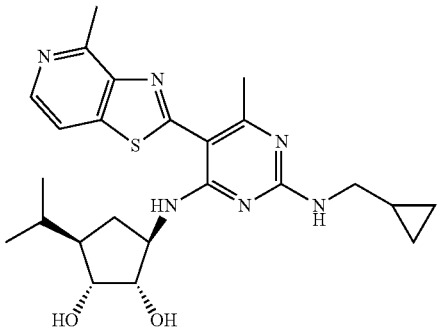
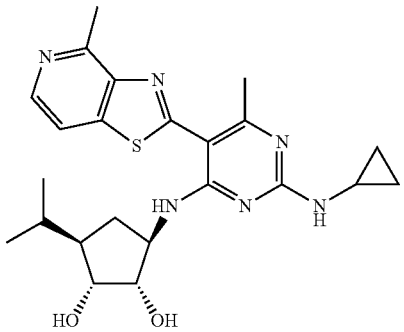
Compd #	Structure	EC90 (μM)	LC-MS or MS
5282		>1.0	572.3
5283		A	487.0
5284		A	469.0
5285		A	455.0

TABLE VI-continued

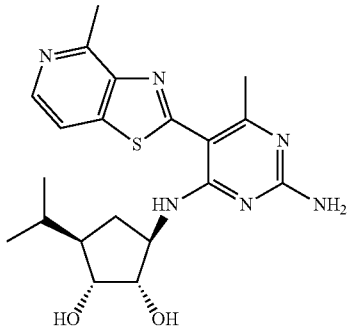
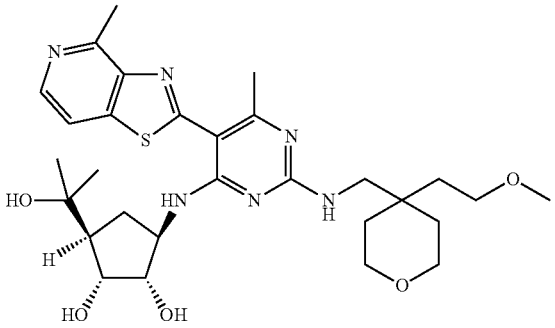
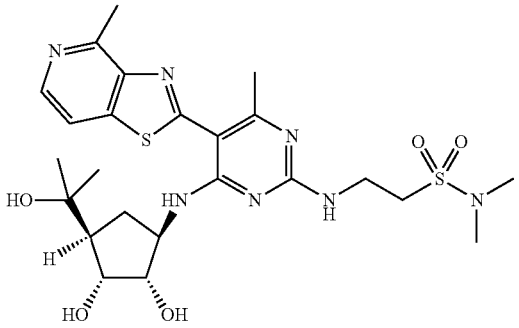
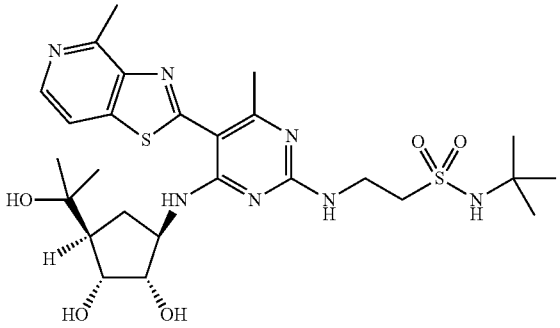
Compd #	Structure	EC90 (μM)	LC-MS or MS
5286		A	415.0
5287		A	587.0
5288		A	566.0
5289		A	594.0

TABLE VI-continued

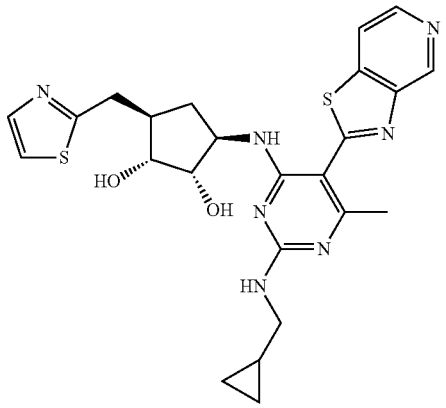
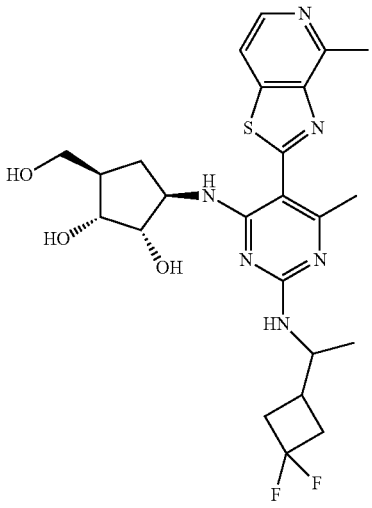
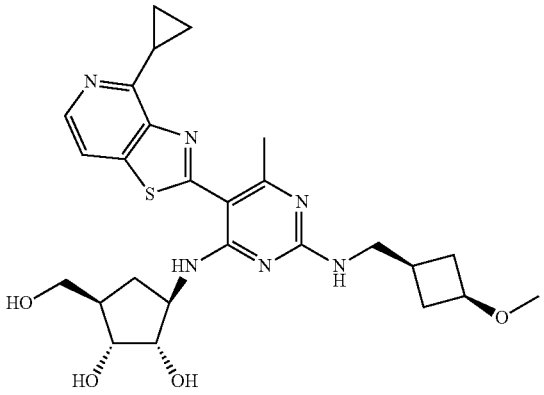
Compd #	Structure	EC90 (μM)	LC-MS or MS
5290		A	510.1
5291		A	521.2
5292		A	527.2

TABLE VI-continued

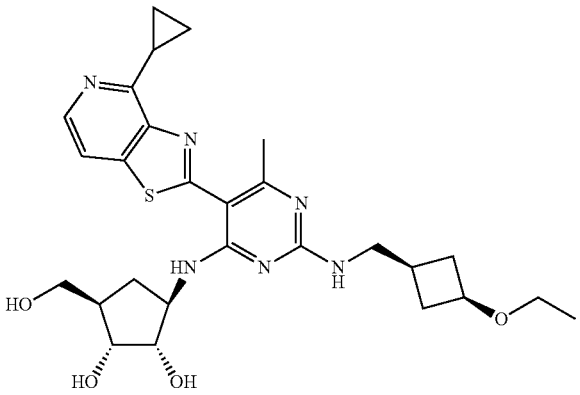
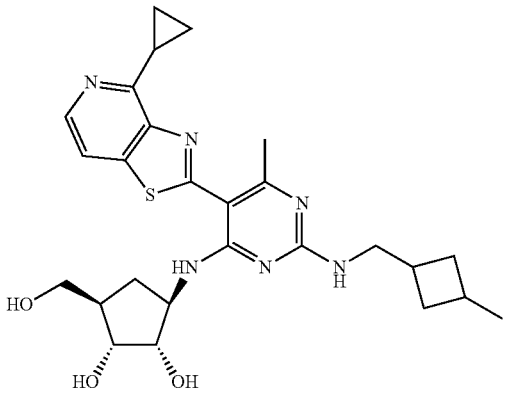
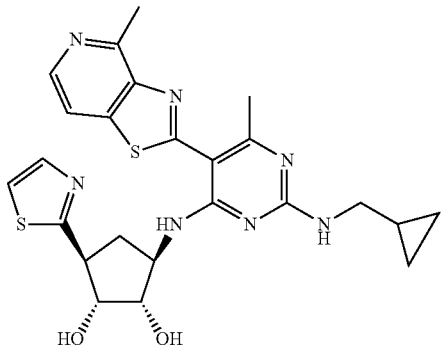
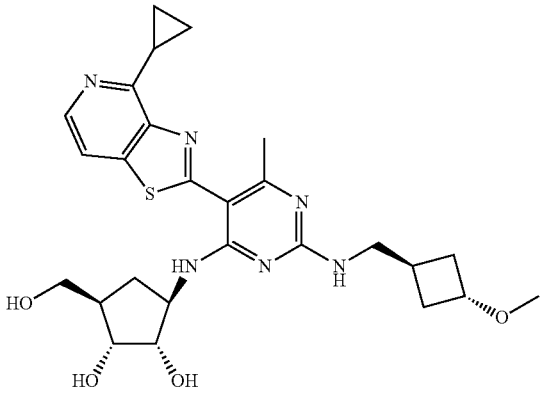
Compd #	Structure	EC90 (μM)	LC-MS or MS
5293		A	541.2
5294		A	511.3
5295		A	510.1
5296		A	527.2

TABLE VI-continued

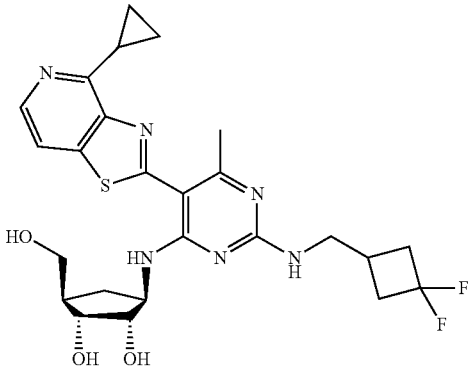
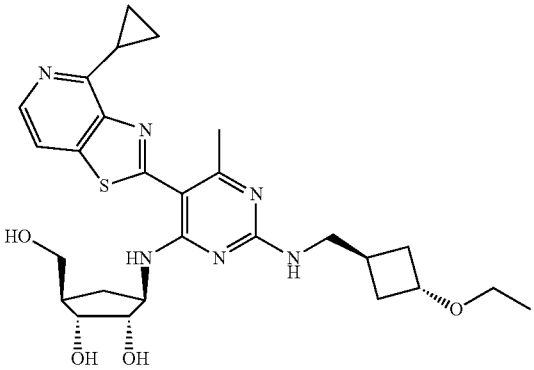
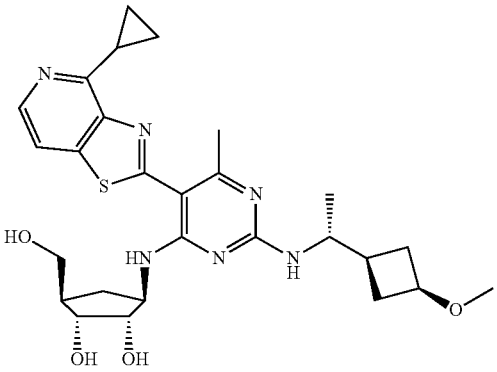
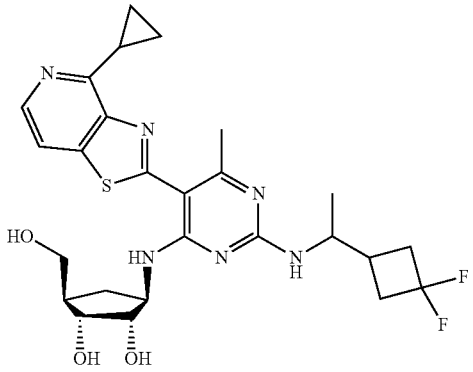
Compd #	Structure	EC90 (μM)	LC-MS or MS
5297		A	533.1
5298		A	541.3
5299		A	541.3
5300		A	547.2

TABLE VI-continued

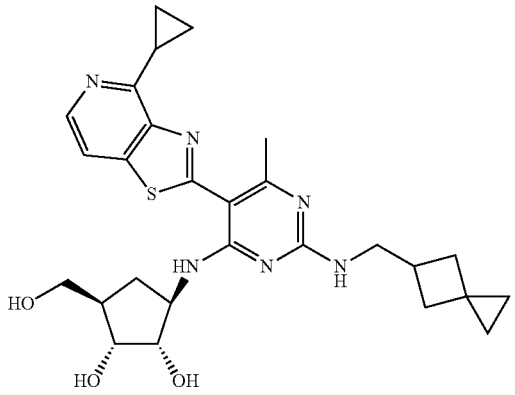
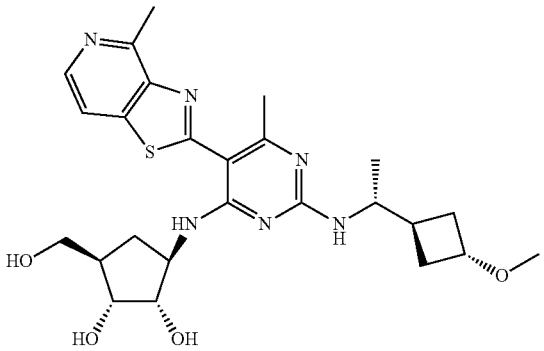
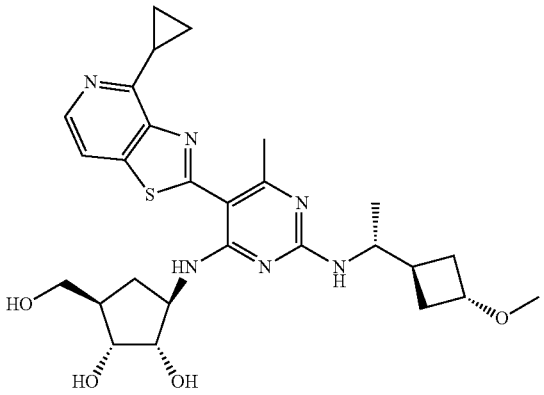
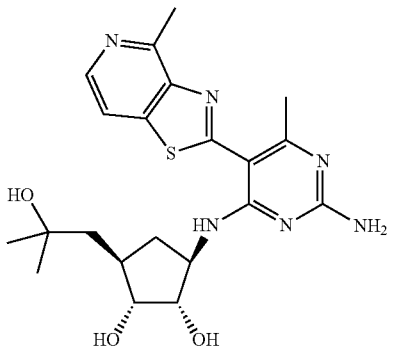
Compd #	Structure	EC90 (μM)	LC-MS or MS
5301		A	523.2
5302		A	515.2
5303		A	541.2
5304		A	445.2

TABLE VI-continued

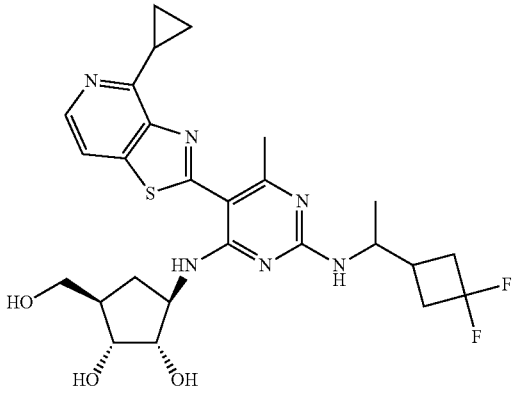
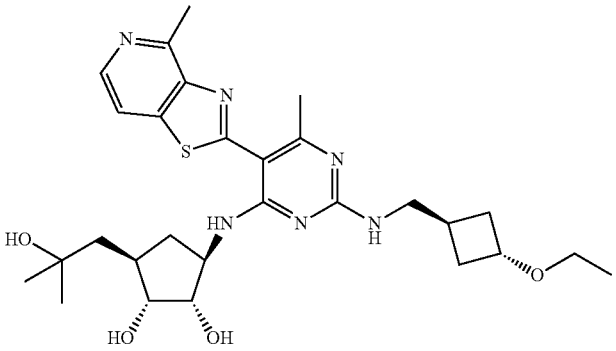
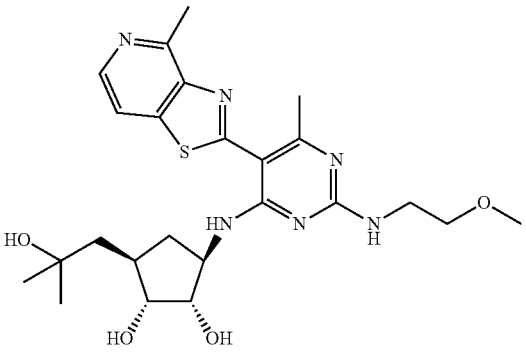
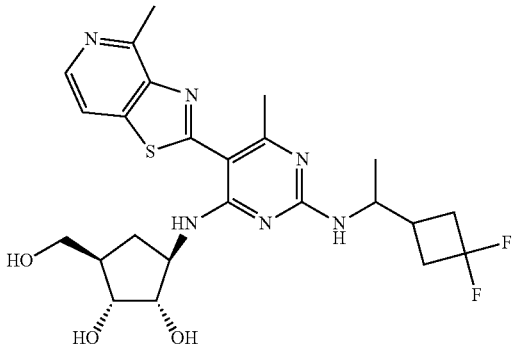
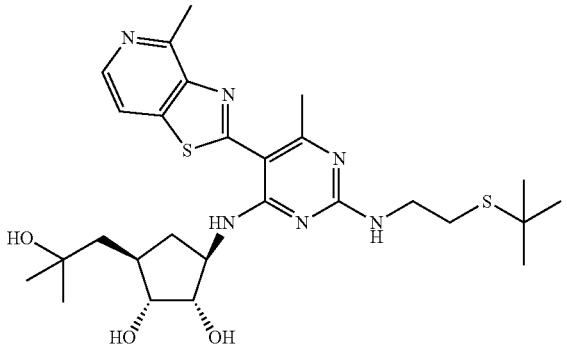
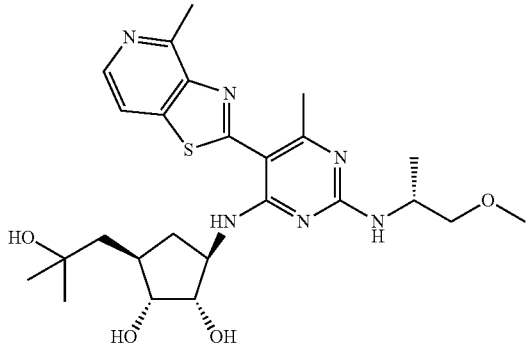
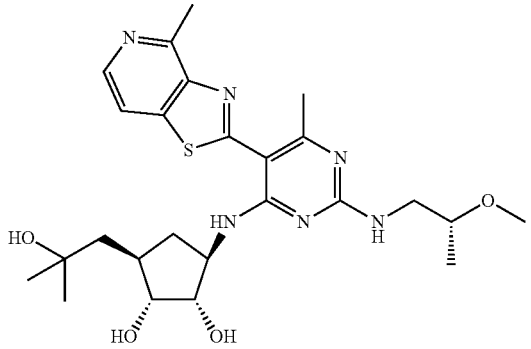
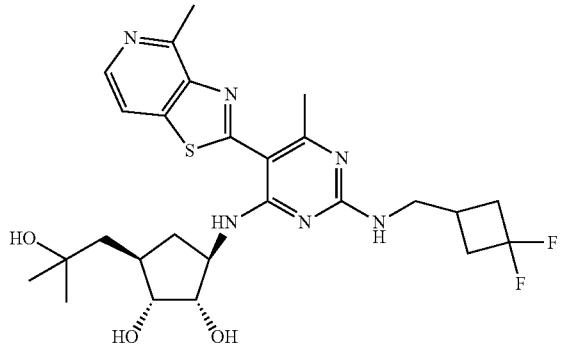
Compd #	Structure	EC90 (μM)	LC-MS or MS
5305		B	547.5
5306		A	557.3
5307		A	503.2
5308		A	521.5

TABLE VI-continued

Compd #	Structure	EC90 (μM)	LC-MS or MS
5309		A	561.2
5310		A	517.2
5311		A	517.2
5312		A	549.2

METHODS OF USE

The compounds of the invention are useful in human and veterinary medicine for treating or preventing a viral infection or a virus-related disorder in a patient. In accordance with the invention, the compounds of the invention can be administered to a patient in need of treatment or prevention of a viral infection or a virus-related disorder.

Accordingly, in one embodiment, the invention provides methods for treating a viral infection in a patient comprising administering to the patient an effective amount of at least one compounds of the invention or a pharmaceutically

acceptable salt, ester, prodrug, isomer, tautomer, or solvate thereof. In another embodiment, the invention provides methods for treating a virus-related disorder in a patient comprising administering to the patient an effective amount of at least one compounds of the invention or a pharmaceutically acceptable salt, ester, prodrug, isomer, tautomer, or solvate thereof.

Treatment or Prevention of a Viral Infection

The compounds of the invention can be used to treat or prevent a viral infection. In one embodiment, the compounds of the invention can be used to inhibit viral replication. In a specific embodiment, the compounds of the invention can be inhibitors of HCV replication. Accordingly, the compounds of the invention are useful for treating viral diseases and disorders related to the activity of a virus, such as HCV polymerase.

Such uses as are described herein may be performed in a patient in need thereof, although in vitro and ex vivo uses, such as in diagnostic and research contexts, are also contemplated. References made herein to the use of compounds of the invention also refers to uses of compositions comprising compounds of the invention.

Examples of viral infections that can be treated or prevented using the present methods, include but are not limited to, hepatitis A infection, hepatitis B infection and hepatitis C infection.

In one embodiment, the viral infection is hepatitis C infection.

In one embodiment, the hepatitis C infection is acute hepatitis C. In another embodiment, the hepatitis C infection is chronic hepatitis C.

The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland et al., *Pathology,* 30(2):192-195 (1998). The nomenclature set forth in Simmonds et al., *J Gen Virol,* 74 (Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, e.g., 1a, 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see Lamballerie et al, *J Gen Virol,* 78 (Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds et al., *J Gen Virol,* 75 (Pt 5):1053-1061 (1994)).

Treatment or Prevention of a Virus-Related Disorder

The compounds of the invention can be used to treat or prevent a virus-related disorder. Accordingly, the compounds of the invention are useful for treating disorders related to the activity of a virus, such as liver inflammation or cirrhosis. Virus-related disorders include, but are not limited to, RNA-dependent polymerase-related disorders and disorders related to HCV infection.

Treatment or Prevention of a RNA-Dependent Polymerase-Related Disorder

The compounds of the invention are useful for treating or preventing a RNA dependent polymerase (RdRp) related disorder in a patient. Such disorders include viral infections wherein the infective virus contain a RdRp enzyme.

Accordingly, in one embodiment, the present invention provides a method for treating a RNA dependent polymerase-related disorder in a patient, comprising administering to the patient an effective amount of at least one compounds of the invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Disorder Related to HCV Infection

The compounds of the invention can also be useful for treating or preventing a disorder related to an HCV infection. Examples of such disorders include, but are not limited to, cirrhosis, portal hypertension, ascites, bone pain, varices, jaundice, hepatic encephalopathy, thyroiditis, porphyria cutanea tarda, cryoglobulinemia, glomerulonephritis, sicca syndrome, thrombocytopenia, lichen planus and diabetes mellitus.

Accordingly, in one embodiment, the invention provides methods for treating an HCV-related disorder in a patient, wherein the method comprises administering to the patient a therapeutically effective amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Combination Therapy

In another embodiment, the present methods for treating or preventing a viral infection can further comprise the administration of one or more additional therapeutic agents. In one embodiment, such one or more additional therapeutic agent may be one or more additional compounds of the invention. In another embodiment, such one or more additional therapeutic agent is an agent other than a compound of the invention.

In one embodiment, the additional therapeutic agent is an antiviral agent. Non-limiting examples of antiviral agents are as described herein and include, e.g., interferon.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a patient, the method comprising administering to the patient: (i) at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) at least one antiviral agent other than a compound of the invention, wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering such a combination to a patient, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a compound of the invention and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like). (A commercial example of such single dosage unit containing fixed amounts of two different active compounds is VYTORIN® (available from Merck Schering-Plough Pharmaceuticals, Kenilworth, N.J.)).

In one embodiment, the at least one compound of the invention is administered at time when the additional antiviral agent(s) exert their prophylactic or therapeutic effect, or vice versa.

In another embodiment, the at least one compound of the invention and the additional antiviral agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, the at least one compound of the invention and the additional antiviral agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, the at least one compound of the invention and the additional antiviral agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, the at least one compound of the invention and the additional antiviral agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

The at least one compound of the invention and the additional antiviral agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

In one embodiment, the administration of at least one compound of the invention and the additional antiviral agent(s) may inhibit the resistance of a viral infection to these agents.

Non-limiting examples of other therapeutic agents useful in the present compositions and methods include an an viral (e.g., HCV) polymerase inhibitor, a viral (e.g., HCV) protease inhibitor, an interferon, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral protease inhibitor, a virion production inhibitor, an immunosuppressive agent, an antiviral antibody, a CYP-450 inhibitor, an antiviral booster, and an antiviral sensitizer, and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the at least one additional antiviral agent is a viral polymerase inhibitor.

In another embodiment, the at least one additional antiviral agent is an HCV polymerase inhibitor.

In one embodiment, the at least one additional antiviral agent is a viral protease inhibitor.

In another embodiment, the at least one additional antiviral agent is an HCV protease inhibitor.

In another embodiment, the at least one additional antiviral agent is an interferon.

In still another embodiment, the at least one additional antiviral agent is a viral replication inhibitor.

In another embodiment, the at least one additional antiviral agent is an antisense agent.

In another embodiment, the at least one additional antiviral agent is a therapeutic vaccine.

In a further embodiment, the at least one additional antiviral agent is an virion production inhibitor.

In another embodiment, the at least one additional antiviral agent is an antibody.

In another embodiment, the at least one additional antiviral agents comprise a protease inhibitor and a polymerase inhibitor.

In still another embodiment, the at least one additional antiviral agents comprise a protease inhibitor and an immunosuppressive agent.

In yet another embodiment, the at least one additional antiviral agents comprise a polymerase inhibitor and an immunosuppressive agent.

In a further embodiment, the at least one additional antiviral agents comprise a protease inhibitor, a polymerase inhibitor and an immunosuppressive agent.

In another embodiment the at least one additional agent is ribavirin, Levovirin, or Viramidine.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention and a CYP-450 inhibitor. Non-limiting examples of suitable CYP-450 inhibitors include ritonavir.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention and an interferon. Non-limiting examples of such interferon are as described herein and include alpha interferon, pegylated interferon and conjugates thereof. Additional non-limiting examples of interferon include PEG-Intron™ brand pegylated interferon, Pegasys™ brand pegylated interferon, Infergen™ brand interferon, and Alferon™ brand pegylated interferon.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention and an interferon. Further comprising ribavirin, Levovirin, or Viramidine.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention and a protease inhibitor.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a protease inhibitor, and an interferon.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a protease inhibitor, an interferon, and ribavirin.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a polymerase inhibitor, and an interferon.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a polymerase inhibitor, an interferon, and ribavirin.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a protease inhibitor, polymerase inhibitor, and an interferon.

In other embodiments, pharmaceutical compositions according to the invention comprise at least one compound of the invention, a protease inhibitor, a polymerase inhibitor, an interferon, and ribavirin.

HCV polymerase inhibitors useful in the present methods and compositions include, but are not limited to VP-19744 (Wyeth/ViroPharma), HCV-796 (Wyeth/ViroPharma), NM-283 (Idenix/Novartis), R-1626 (Roche), MK-0608 (Merck), A848837 (Abbott), GSK-71185 (Glaxo Smith-Kline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni et al., *Current Opinion in Drug Discovery and Development,* 7(4):446 (2004); Tan et al., *Nature Reviews,* 1:867 (2002); and Beaulieu et al., *Current Opinion in Investigational Drugs,* 5:838 (2004).

Additional non-limiting examples of HCV polymerase inhibitors useful in the present methods and compositions

include: MK00608, NM283, HCV796, R1626, A848837, GSK71185, R7128, VCH759, GS9190, VP19744, and XTL2125.

Additional non-limiting examples of HCV polymerase inhibitors useful in the present methods and compositions include: R803 (Rigel Pharmaceuticals), PSI-7977 (Phramasset), and RG7128 (Roche/Pharmasset & Intermune).

Additional non-limiting examples of HCV polymerase inhibitors and HCV protease inhibitors useful in the present methods and compositions include: ANA598 (Anadys Pharmaceuticals), ABT-333, (Abbott), VCH-916, (Virochem), MK7009, (Merck), PF-00868554, (Pfizer) VX-500, (Vertex) GS9190, (Gilead) GSK625433, (GlazoSmithKline) ITMN-191 (R-7227), (Intermune), RG7128, (Pharmasset/Roche), VCH-759 (Virochem), R1626, (Roche), TMC435350, (Medivir/Tibotec), SCH 503034 (Boceprevir) (Schering), SCH900518 (Schering), and VX 950 (telaprevir) (Vertex). Additional non-limiting examples of HCV polymerase inhibitors include MK-3281 (Merck), PSI-7851 (Pharmasset), IDX184 (Indenix), ANA598 (Anadys), ABT-333 (Abbott), VCH-916 (Vertex), PF-0086554 (Pfizer), R7128 (Pharmasset/Roche), GS 9190 (Gilead), and VCH-759 (Vertex).

Additional non-limiting examples of agents useful in the present methods and compositions include: SPC3649 (LNA-antimiR™-122), microRNA, Santaris Pharma, CF102, (A3AR AGONISTS) (CAN-FITE), IMO-2125, TLR9 agonist, (Idera Pharmaceuticals), PYN17, Botanical, (Phynova), Bavituximab (formerly Tarvacin), Anti-Phospholipid Therapy, (Peregrine), A-831 and/or A-832 (each of which are listed as NS5A Inhibitors from ArrowTherapeutics Ltd.), BMS-790052 (NS5A inhibitors from BMS), NOV-205, Immunomodulator, (Novelos Therapeutics), CTS-1027, Anti-inflammatory, (Conatus), Oglufanide disodium, Immunomodulator, (Implicit Bioscience), Alinia (nitazoxanide), Thiazolides, (Romark Laboratories), SCV-07, Broad spectrum immune stimulator, (SciClone), MitoQ (mitoquinone), Inflammation/Fibrosis Inhibitor, (Antipodean Pharmaceuticals), DEBIO-025, Cyclophilin inhibitor, (Debio Pharm Group), SCY-635, cyclophilin inhibitor (SCYNEXIS), PF-03491390 (Formerly IDN-6556), Pancaspase Inhibitor, (Pfizer Pharmaceuticals), Civacir, HCV Immune Globulin, NABI, MX-3253 (celgosivir), Glucosidase I Inhibitor, (MIGENIX), VGX-410C (Mifepristone), IRES Inhibitor, (VGX Pharmaceuticals), Viramidine (Taribavirin), Nucleoside Analogue, (Valeant Pharmaceuticals), and ZADAXIN® (thymalfasin or thymosin alpha 1), Immunomodulator, (SciClone/Sigma-Tau).

Additional non-limiting examples of agents useful in the present methods and compositions include: TLR agonists (e.g., ANA773, Anadys Pharmaceuticals), immunomodulators (e.g., CYT107, Cytheris; oglufanide disodium, Implicit Bioscience), microRNA (e.g., SPC3649 (LNA-antimiR™-122, Santaris Pharma), A3AR agonists (e.g., CF102, CAN-FITE), TLR9 agonists (e.g., Idera Pharmaceuticals), antiphospholipid therapeutics (e.g., bavituximab (formerly Tarvacin), Peregrine), immunomodulators (e.g., NOV-205, Novelos Therapeutics), caspase inhibitors (e.g., GS-9450, Gilead), anti-inflammatories (e.g., CTS-1027, Conatus), thiazolides (e.g., alinia (nitazoxanide), Romark Laboratories), broad spectrim immune stimulators (e.g., SCV-07, SciClone), inflammation/fibrosis inhibitors (e.g., MitoQ (mitoquinone), Antipodean Pharmaceuticals, cyclophilin inhibitors (e.g., DEBIO-025, Debio Pharm Group), pancaspase inhibitors (e.g., PF-03491390 (formerly IDN-6556, Pfizer Pharmaceuticals), and nucleoside analogues (e.g., Viramidine (Taribavirin), Valeant Pharmaceuticals).

Interferons useful in the present methods and compositions include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, Hoffman La-Roche, Nutley, N.J.) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, Boehringer Ingelheim, Ingelheim, Germany), interferon alpha fusion polypeptides, or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, Amgen, Thousand Oaks, Calif.).

Additional examples of Interferons useful in the present methods and compositions include, but are not limited to: IL-29 (PEG-Interferon Lambda), Long acting Interferon, ZymoGenetics, Oral Interferon alpha, Oral Interferon, (Amarillo Biosciences), Belerofon (oral), Oral interferon, (Nautilus Biotech), BLX-883 (Locteron), Long Acting Interferon, (Biolex Therapeutics/OctoPlus), Omega Interferon, Interferon, (Intarcia Therapeutics), Albuferon, Long Acting Interferon (injections every two weeks), (Human Genome Sciences), Consensus interferon (Infergen), and Interferon, (Three Rivers Pharma).

Antiviral antibodies (antibody therapy agents) useful in the present methods and compositions include, but are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like). Viral protease inhibitors useful in the present methods and compositions include, but are not limited to, NS3 serine protease inhibitors (including, but are not limited to, those disclosed in U.S. Pat. Nos. 7,012,066, 6,914,122, 6,911,428, 6,846,802, 6,838,475, 6,800,434, 5,017,380, 4,933,443, 4,812,561 and 4,634,697; and U.S. Patent Publication Nos. US20020160962, US20050176648 and US20050249702), HCV protease inhibitors (e.g., SCH503034 (Schering-Plough), VX-950 (Vertex), GS-9132 (Gilead/Achillion), ITMN-191 (InterMune/Roche)), and HIV protease inhibitors (e.g., amprenavir, atazanavir, fosemprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir and TMC114).

Viral replication inhibitors useful in the present methods and compositions include, but are not limited to, NS3 helicase inhibitors, NS5A inhibitors, ribavirin, viramidine, A-831 (Arrow Therapeutics); an antisense agent or a therapeutic vaccine.

In one embodiment, viral replication inhibitors useful in the present methods and compositions include, but are not limited to, NS3 helicase inhibitors or NS5A inhibitors.

Examples of protease inhibitors useful in the present methods include, but are not limited to, an HCV protease inhibitor and a NS-3 serine protease inhibitor.

Examples of NS-3 serine protease inhibitors include, but are not limited to, SCH 503034 (Boceprevir) (Schering), SCH900518 (Schering), Telaprevir (VX950), ITMN-191, TMC435350, GS9132, MK7009, and BILN2061.

Examples of HCV protease inhibitors useful in the present methods include, but are not limited to, those disclosed in

Landro et al., *Biochemistry,* 36(31):9340-9348 (1997); Ingallinella et al., *Biochemistry,* 37(25):8906-8914 (1998); Llinás-Brunet et al., *Bioorg Med Chem Lett,* 8(13):1713-1718 (1998); Martin et al., *Biochemistry,* 37(33):11459-11468 (1998); Dimasi et al., *J Virol,* 71(10):7461-7469 (1997); Martin et al., *Protein Eng,* 10(5):607-614 (1997); Elzouki et al., *J Hepat,* 27(1):42-48 (1997); *BioWorld Today,* 9(217):4 (Nov. 10, 1998); and International Publication Nos. WO 98/14181; WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734. Additional non-limiting examples of protease inhibitors include ACH-1625 (Achillion), ABT-450 (Abbott/Enanta), BI201335 (Boehringer Ingelheim Pharma), VX-813 & VX-500 (Vertex), PHX1766 (Phenomix), VX-500 (Vertex), ITMN-191 (R-7227) (InterMune), MK7009 (Merck), BI 207127 (Boerhinger Ingelheim), SCH 503034 (Boceprevir) (Schering), SCH900518 (Schering), TMC435 (Medivir/Tibotec), Telapravir (VX950) and (Vertex), XTL-2125 (XTL Biopharmaceuticals), PHX1766 (Phenomix), TMC-435 (Medvir/Tibotec).

Additional examples of other therapeutic agents useful in the present methods and compositions include vaccines. Non-limiting examples of antiviral vaccines include: ChronVac-C, DNA-based Therapeutic Vaccine, (Inovio/Tripep), TG4040, Therapeutic Vaccine, (Transgene), PeviPRO™, Therapeutic vaccine, (Pevion Biotect), HCV/MF59, Vaccine (s), (Chiron/Novartis), GI-5005, Therapeutic Vaccine, (Globe Immune), IC41, Therapeutic Vaccine, (Intercell), HCV/MF59 (Chiron/Novartis), GI-5005 (Globe Immune), and Civacir (NABI).

Additional examples of other therapeutic agents useful in the present methods and compositions include anti-cancer agents. Non-limiting examples of antiviral anti-cancer agents include: Z10-101, Anti-Liver Cancer (Arsenic), (Ziopharm Oncology), GV1001 (Heptovax), Anti-Liver Cancer, (Pharmexa), PI-88, Anti-liver cancer, (Progen Industries), Nexavar (sorafenib), Anti-liver cancer, (Onyx Pharmaceuticals), and ThermoDox (doxorubicin), Anti-liver cancer, (Celsion). Additional non-limiting examples of viral anticancer agents include CF102 (Can-Fite BioPharma), ZIO-101 (Ziopharm Oncology), GV1001 (Heptovax) (Pharmexa), PI-88 (Progen Industries), ThermoDox (doxorubicin) (Celsion), and Nexavar (sorafenib) (Onyx Pharmaceuticals).

Additional examples of other therapeutic agents useful in the present compositions and methods include, but are not limited to, Levovirin™ (ICN Pharmaceuticals, Costa Mesa, Calif.), VP50406™ (Viropharma, Incorporated, Exton, Pa.), ISIS14803™ (ISIS Pharmaceuticals, Carlsbad, Calif.), Heptazyme™ (Ribozyme Pharmaceuticals, Boulder, Colo.), VX950™ (Vertex Pharmaceuticals, Cambridge, Mass.), Thymosin™ (SciClone Pharmaceuticals, San Mateo, Calif.), Maxamine™ (Maxim Pharmaceuticals, San Diego, Calif.), NKB-122 (JenKen Bioscience Inc., North Carolina), mycophenolate mofetil (Hoffman-LaRoche, Nutley, N.J.).

Additional examples of other therapeutic agents useful in the present methods and compositions include adjunct therapeutics such as thrombopoeitin receiptor antagonists (e.g., LGD-4665, Ligand Pharmaceuticals Inc., and eltromobopag (Promacta), GlaxoSmithKline).

Additional examples of other therapeutic agents useful in the present compositions and methods include, but are not limited to: HCV/MF59, Oral Interferon alpha, Viramidine, Infergen/Consensus, JBK-122, Bavituximab (Tarvacin), Civacir, Albuferon, IL-29 (PEG-Interferon lambda), Omega Interferon, ZADAXIN® (thymalfasin or thymosin alpha 1), NOV-205, PF-03491390 (formerly IDN-6556), Nexavar, ITMN-191, IC41, VX 950 (telaprevir), R1656, MX-3253 (Celgosivir), SCH 503034 (Boceprevir) (Schering), SCH900518 (Schering), Belerofon (oral), VGX-410C, ThermoDox (doxorubicin), R7128, R1626, A-831, DEBIO-025, PeviPRO™, GV1001, PYN17, PI-88, TG4040, BLX-883 (Locteron), ChronVac-R, MitoQ, GSK625433, SOV-07, IMO-2125, Alinia (nitazoxanide), LGD-4665, Z10-101, CF102, VCH-759, VCH-916, Oglufanide disodium, VX-500, TMC435350, PF-00868554, GGI-5005 (Tarmogen), SPC3649 (LNA-antimiR™—122), CTS-1027, ABT-333, Eltrombopag, and ANA598.

Additional examples of other therapeutic agents useful in the present compositions and methods include, but are not limited to adjunct therapeutics. Non-limiting examples include: LGD-4665, Thrombopoeitin Receptor Agonist, (Ligand Pharmaceuticals Inc.), and Eltrombopag (Promacta), Thrombopoeitin Receptor Agonist, (GlaxcoSmithKline).

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a viral infection can be determined by the attending clinician, taking into consideration the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of the viral infection or related disease or disorder. When administered in combination, the compound(s) of the invention and the other agent(s) for treating diseases or conditions listed above can be administered simultaneously (i.e., in the same composition or in separate compositions one right after the other) or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, e.g., one component is administered once daily and another every six hours, or when the preferred pharmaceutical compositions are different, e.g. one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the at least one compound of the invention and the additional antiviral agent(s), when administered as combination therapy, can range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In a further embodiment, the dosage is from about 1 to about 20 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

In one embodiment, when the other therapeutic agent is INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 3MIU (12 mcg)/0.5 mL/TIW is for 24 weeks or 48 weeks for first time treatment.

In another embodiment, when the other therapeutic agent is PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-Plough Corp.), this agent is

administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, for at least 24 weeks.

In another embodiment, when the other therapeutic agent is ROFERON A interferon alpha 2a (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous or intramuscular injection at 3MIU (11.1 mcg/mL)/TIW for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks.

In another embodiment, when the other therapeutic agent is PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous injection at 180 mcg/1 mL or 180 mcg/0.5 mL, once a week for at least 24 weeks.

In another embodiment, when the other therapeutic agent is INFERGEN interferon alphacon-1 (commercially available from Amgen), this agent is administered by subcutaneous injection at 9 mcg/TIW is 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment.

In another embodiment, when the other therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

Compositions and Administration

The compounds of the invention may be used as the neat chemical or as part of a composition, such as a pharmaceutical composition. For example, when administered to a patient, the compounds of the invention can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one compound of the invention and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. anti-inflammatory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more compounds of the invention are in a form suitable for oral administration.

In another embodiment, the one or more compounds of the invention are in a form suitable for intravenous administration.

In another embodiment, the one or more compounds of the invention are in a form suitable for topical administration.

In another embodiment, the one or more compounds of the invention are in a form suitable for sublingual administration.

In one embodiment, a pharmaceutical preparation comprising at least one compound of the invention is formulated in a unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the compound(s) of the invention by weight or volume. In various embodiments, the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the compound(s) of the invention by weight or volume.

The quantity of compound(s) of the invention in a unit dose of preparation may be varied or adjusted from about 0.1 mg to about 2000 mg. In various embodiment, the quantity is from about 1 mg to about 2000 mg, 100 mg to about 200 mg, 500 mg to about 2000 mg, 100 mg to about 1000 mg, and 1 mg to about 500 mg.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24 hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the compound(s) of the invention will be determined according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the compound(s) of the invention range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those described above. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one compound of the invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; (ii) one or more additional therapeutic agents that are not a compound of the invention; and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat a viral infection or a virus-related disorder.

Kits

In another embodiment, the present invention provides a kit comprising a therapeutically effective amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester, isomer, tautomer, or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

In another aspect the present invention provides a kit comprising an amount of at least one compound of the invention, or a pharmaceutically acceptable salt, solvate, ester, isomer, tautomer, or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more ingredients result in a desired therapeutic effect.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein. The entire disclosures of such references are incorporated herein by reference.

Therefore, We claim:

1. A compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

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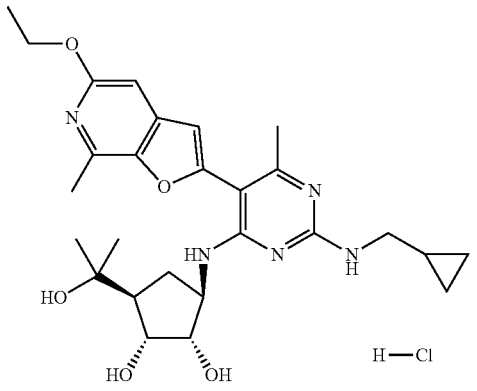
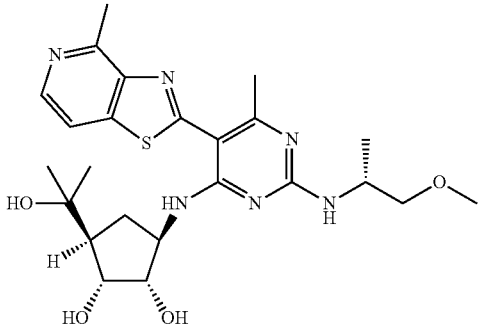
2511	
3137	

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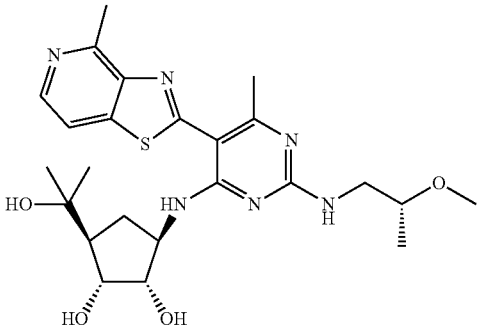
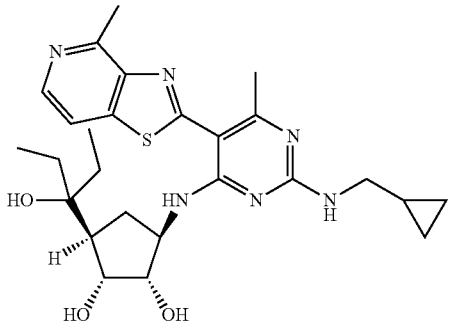
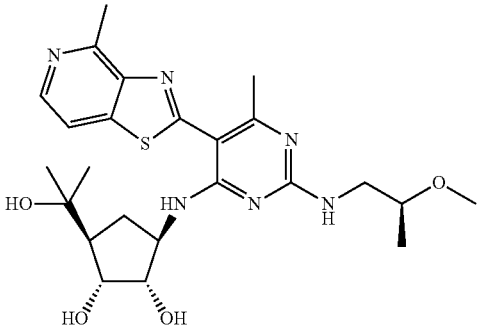
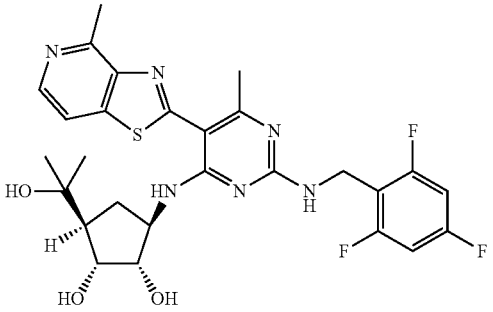
3030	
3182	
3031	
3188	

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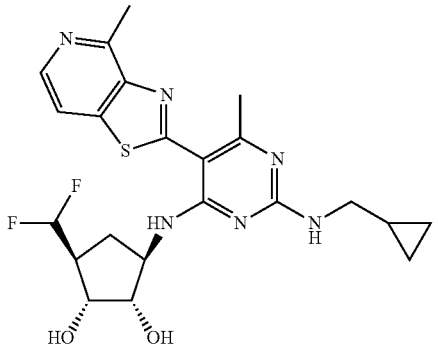
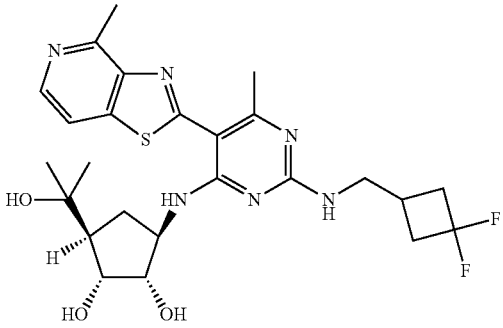
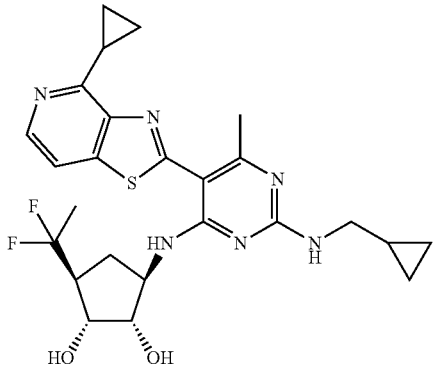
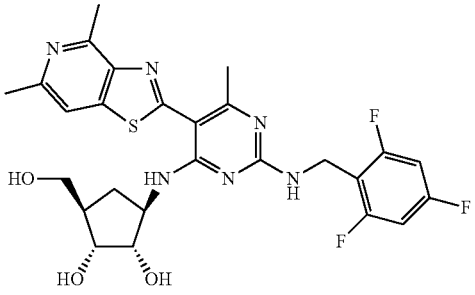
Compd #	Structure
3036	
3239	
3056	
3438	

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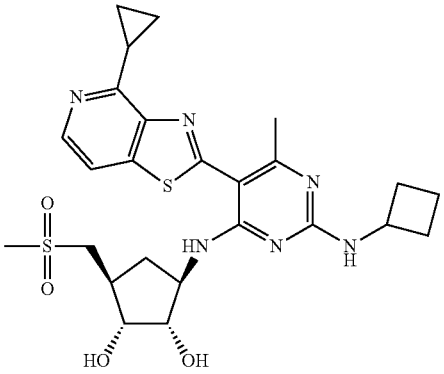
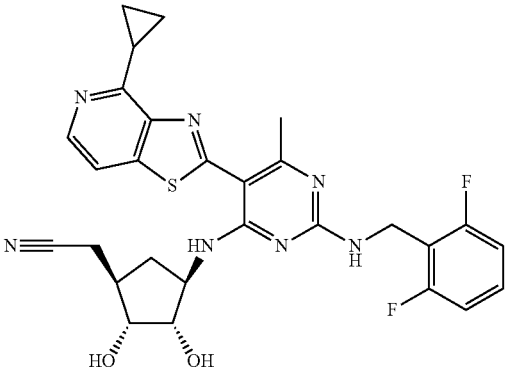
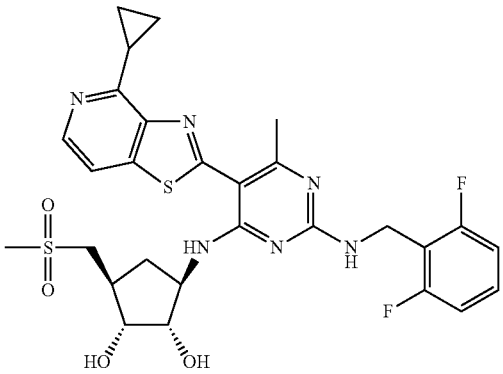
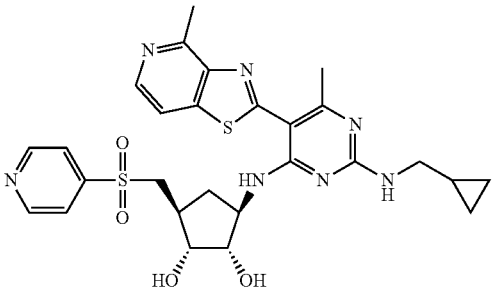
Compd #	Structure
3513	
3569	
3538	
3580	

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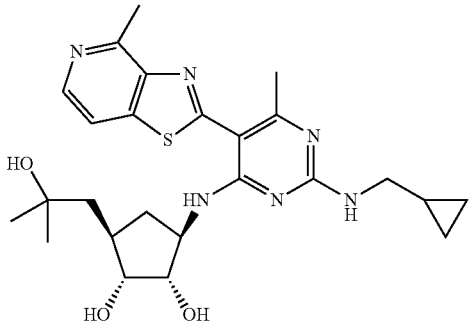
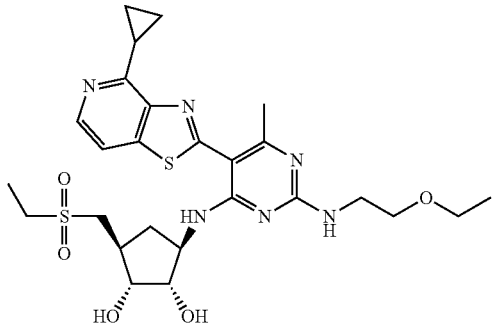
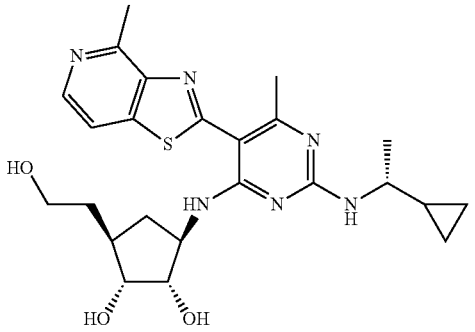
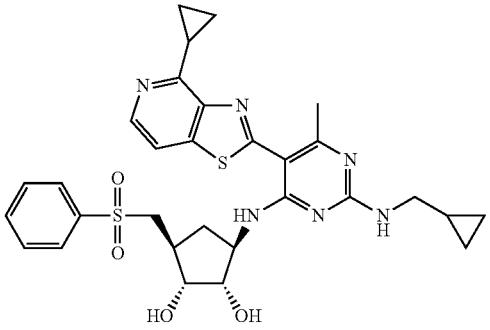
3552	
3721	
3561	
3744	

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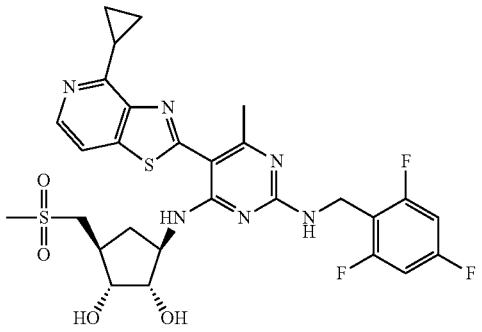
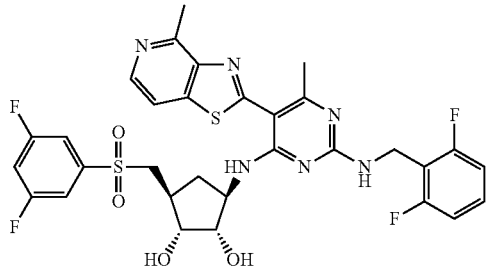
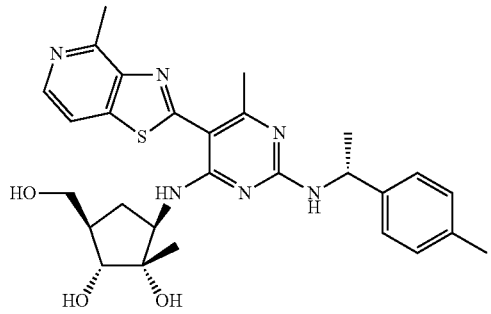
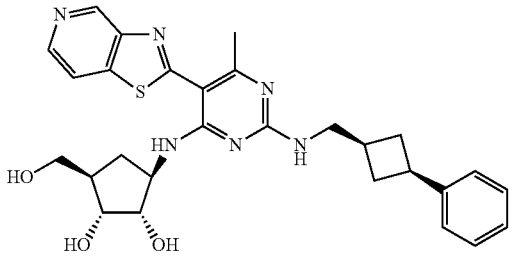
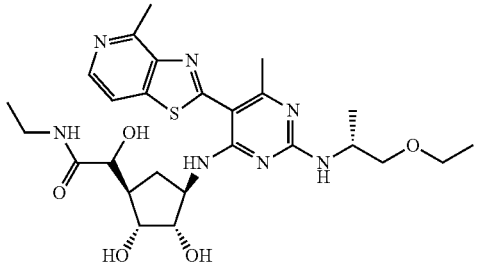
3563	
3754	
3815A	
4512	
4025	

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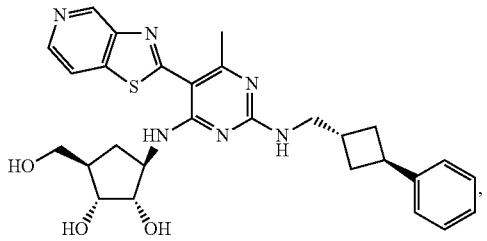
Compd #	Structure
4513	
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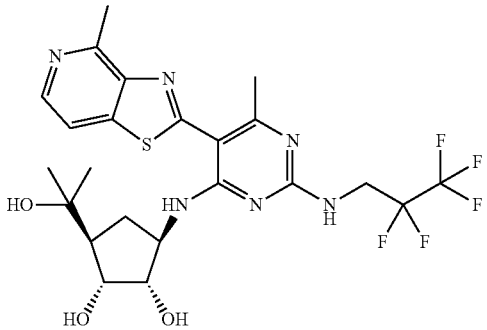
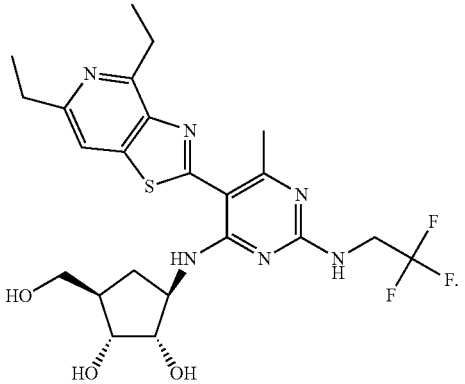
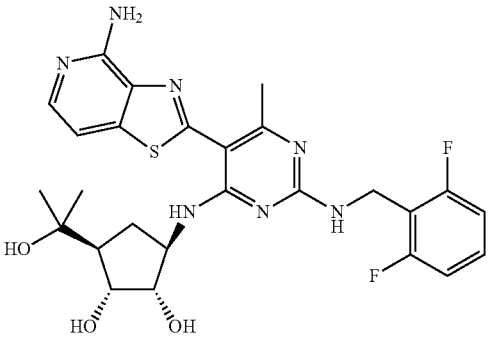
4346	
4706	
4413	

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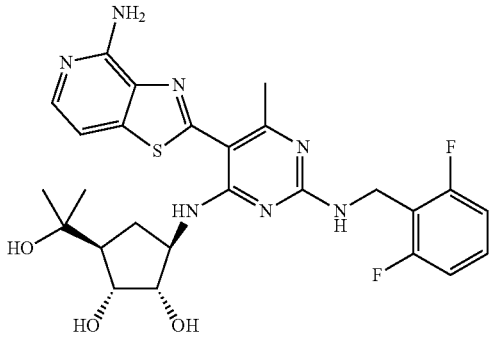
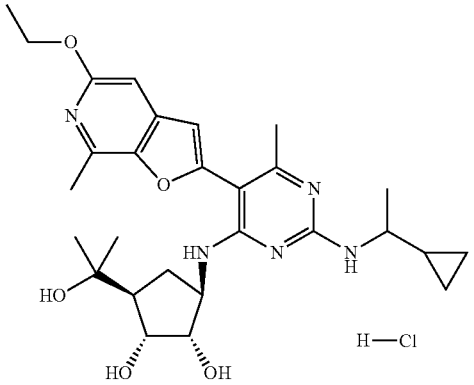
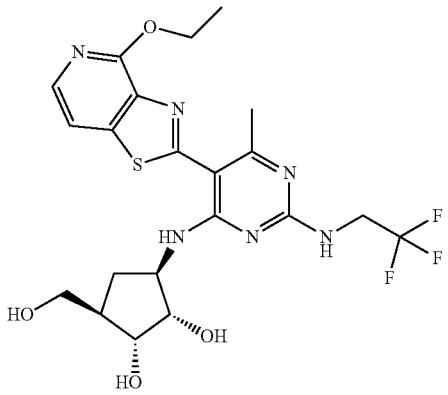
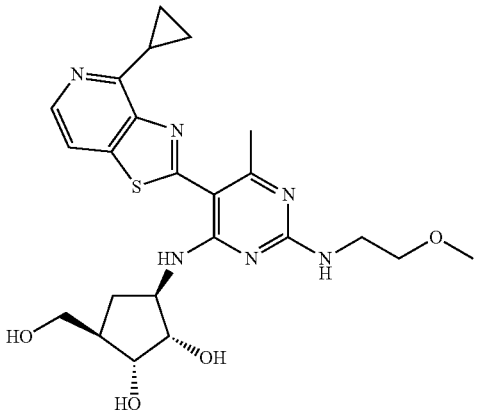
Compd #	Structure
4443	
2415	
2502	
2504	

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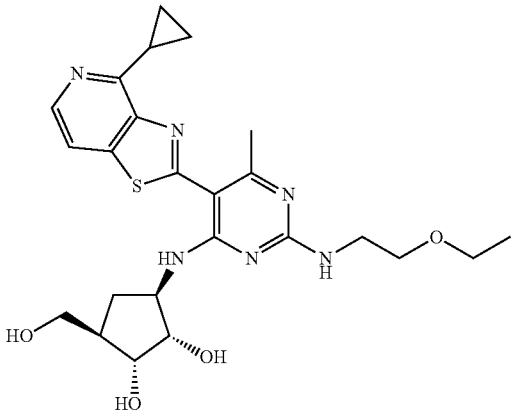
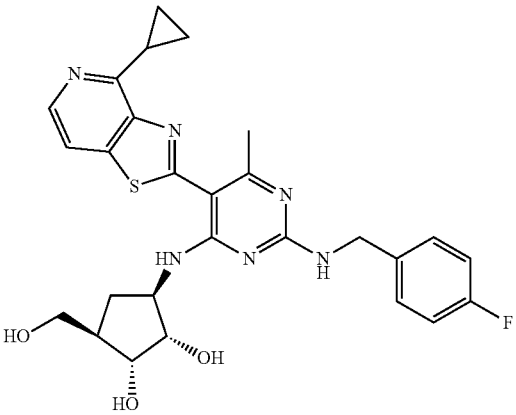
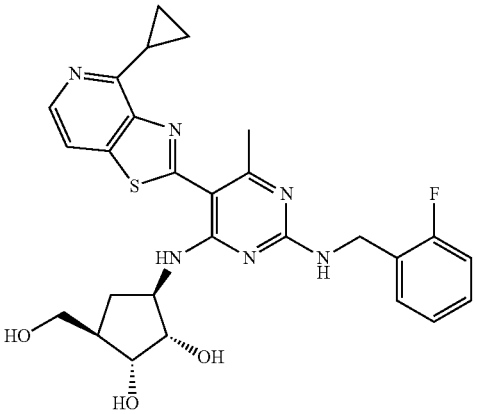
Compd #	Structure
2505	
2508	
2509	

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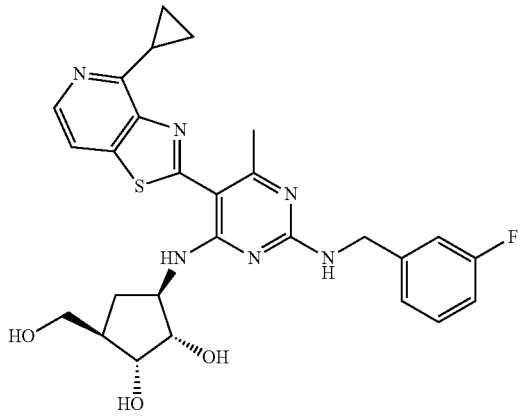
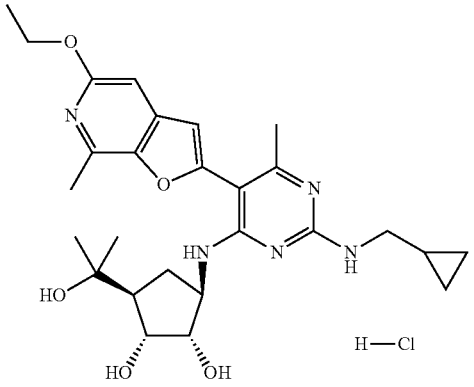
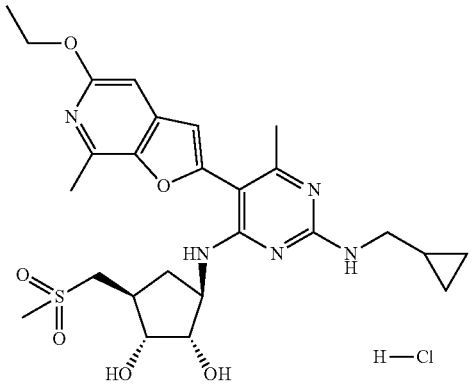
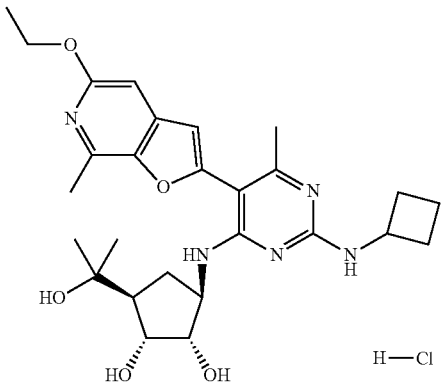
2510	
2511	
2512	
2513	

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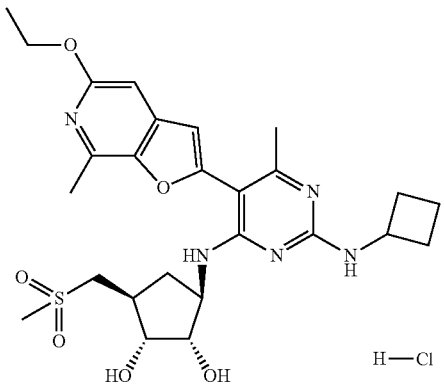
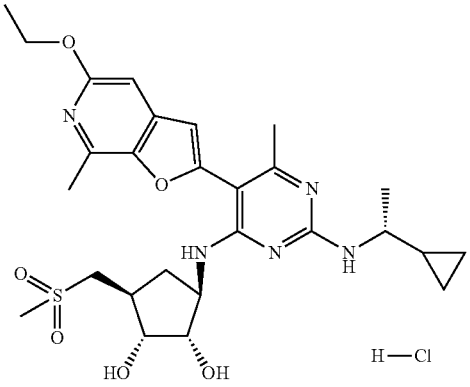
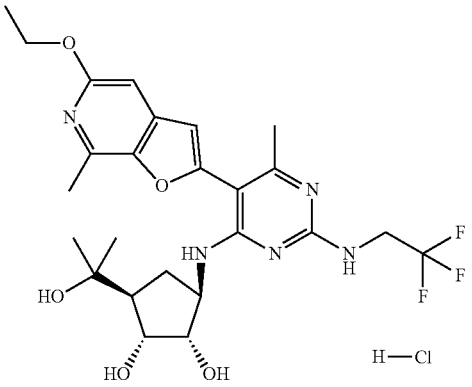
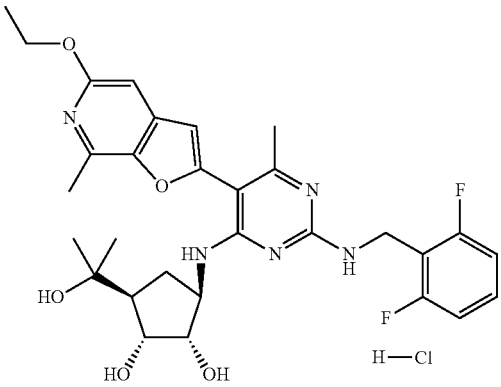
Compd #	Structure
2514	
2516	
2518	
2519	

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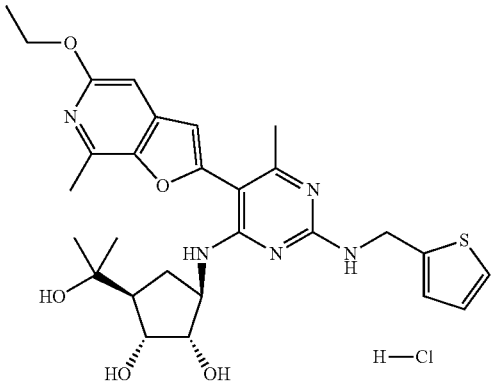
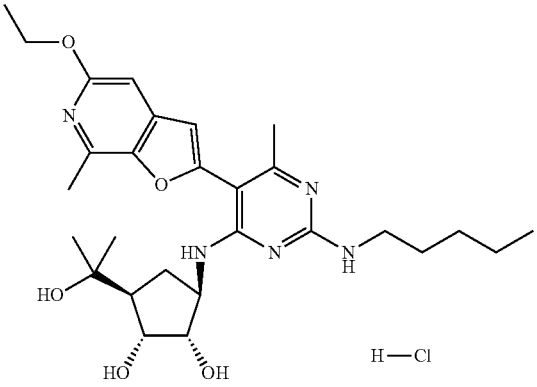
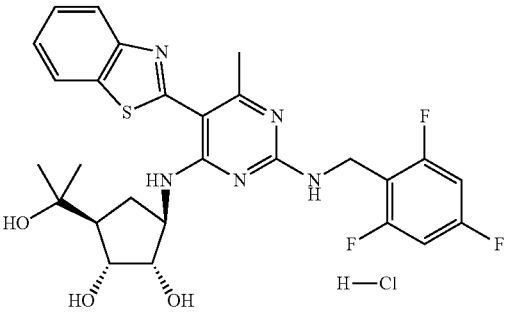
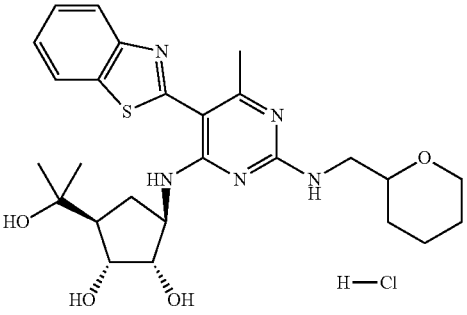
Compd #	Structure
2520	
2521	
2526	
2527	

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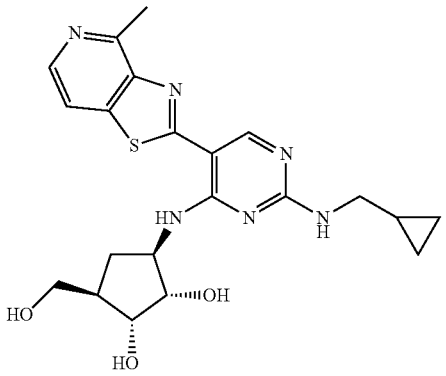
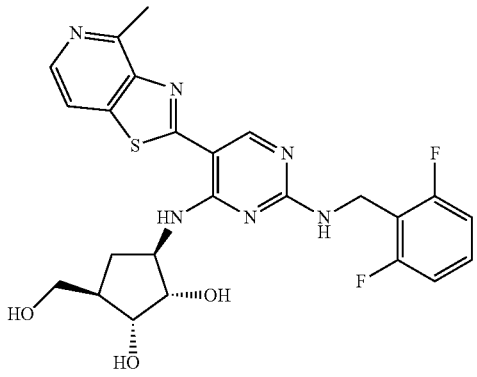
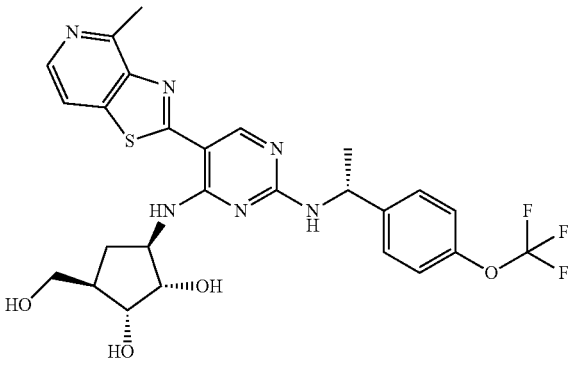
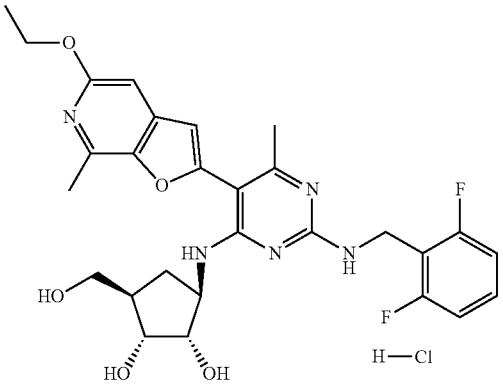
2531	
2532	
2533	
2535	

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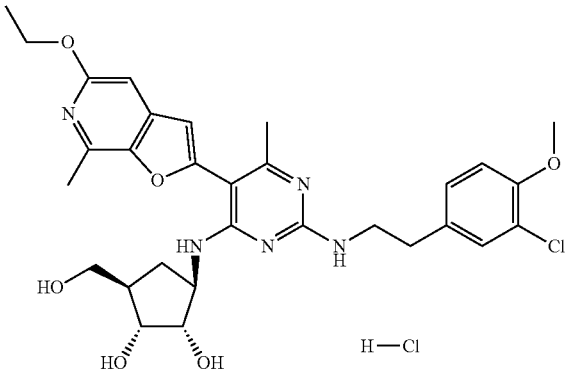
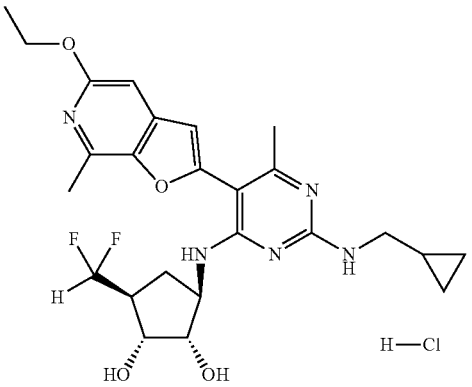
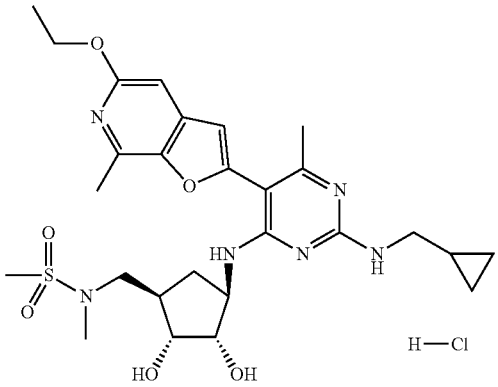
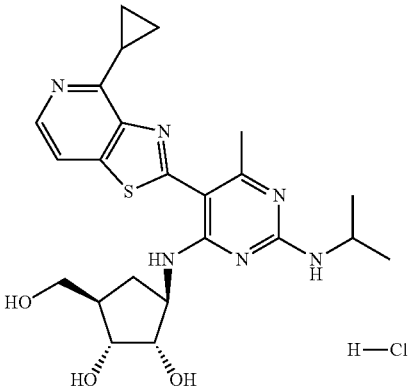
Compd #	Structure
2536	
2537	
2539	
2540	

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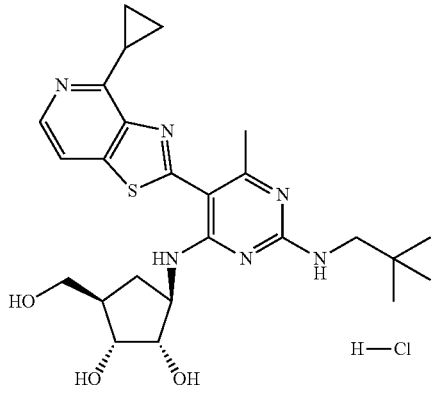
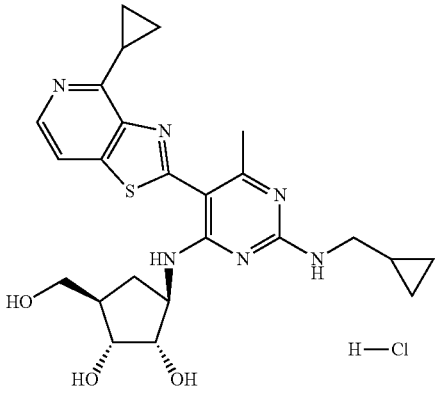
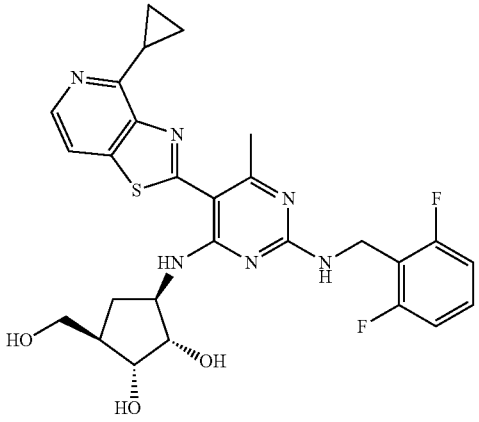
Compd #	Structure
2541	
2542	
2543	

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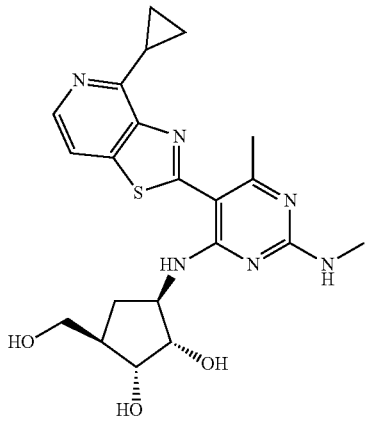
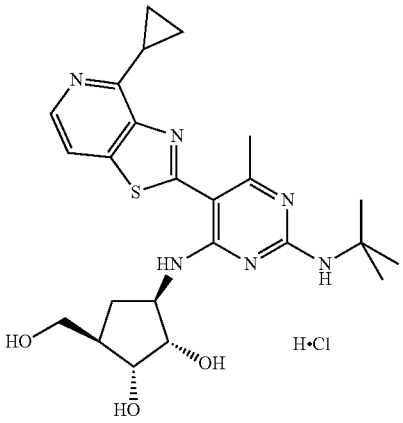
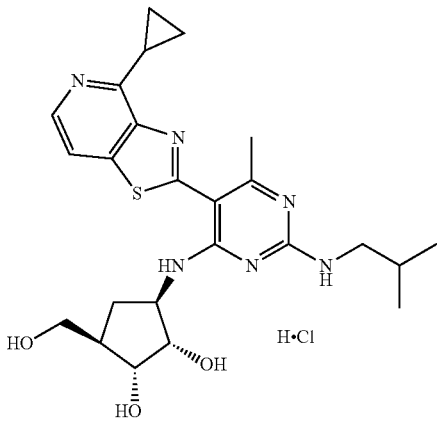
Compd #	Structure
2544	
2545	
2546	

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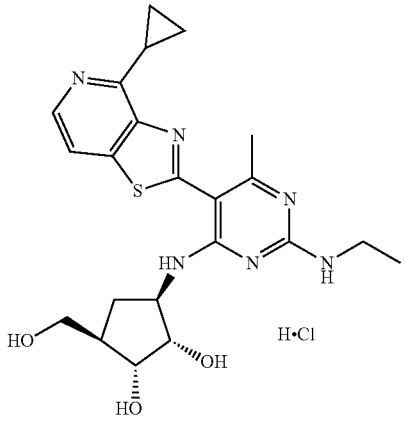
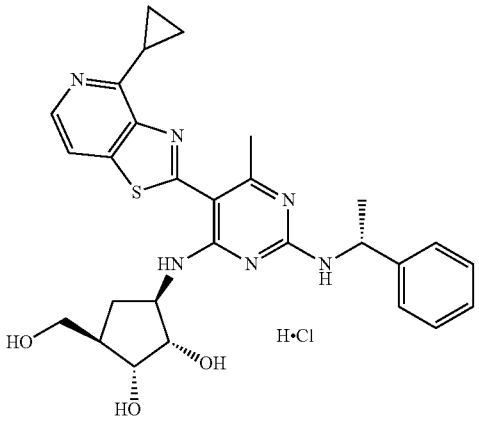
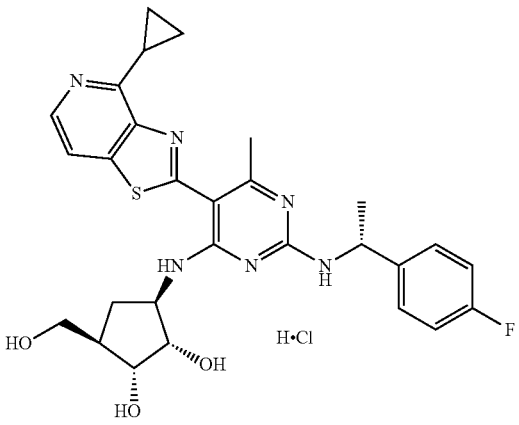
Compd #	Structure
2547	
2549	
2550	

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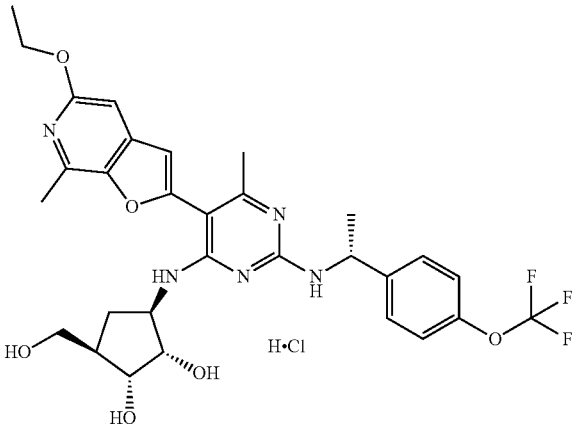
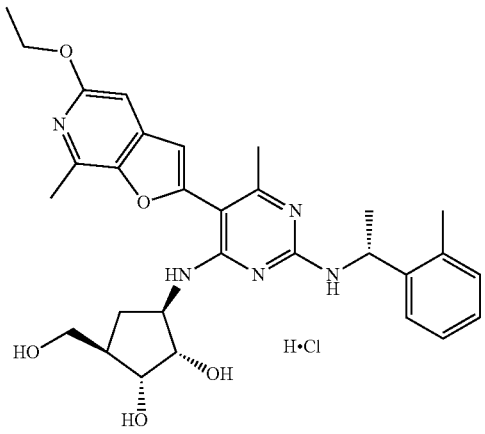
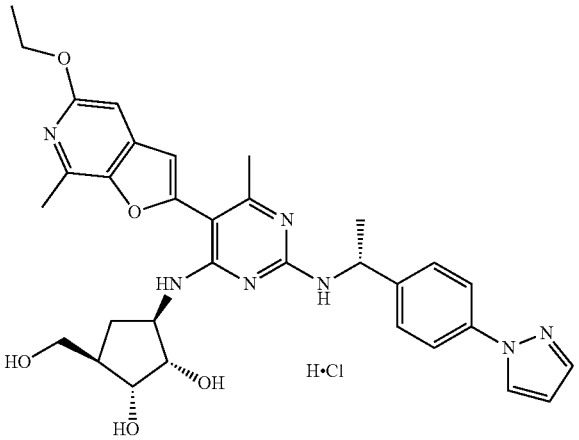
Compd #	Structure
2553	
2555	
2556	

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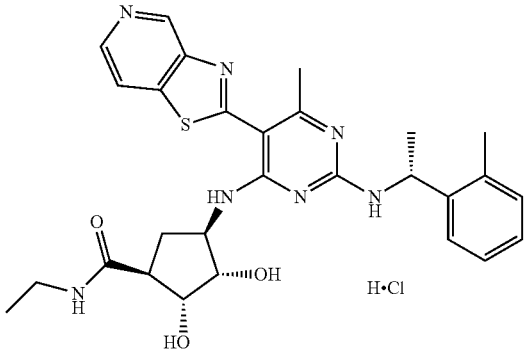
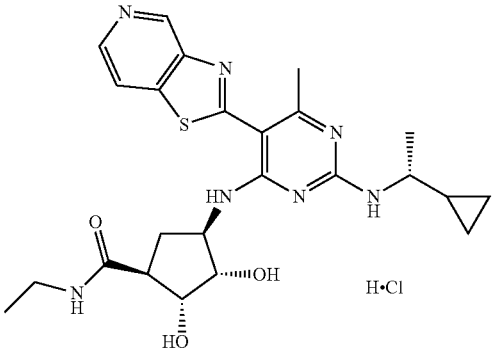
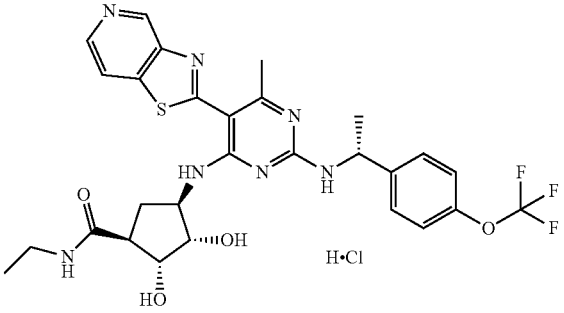
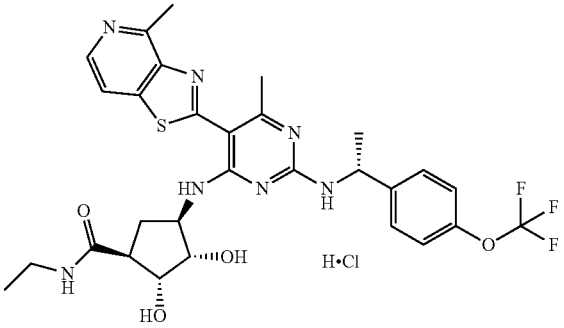
Compd #	Structure
2559	
2562	
2563	
2564	

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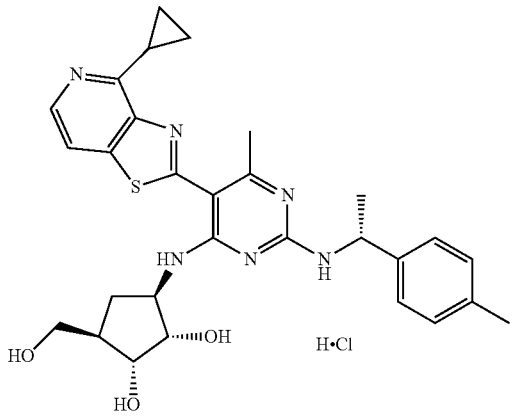
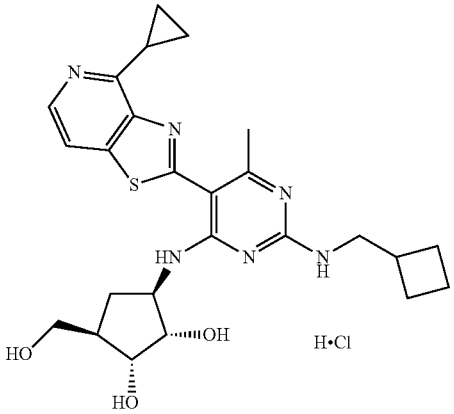
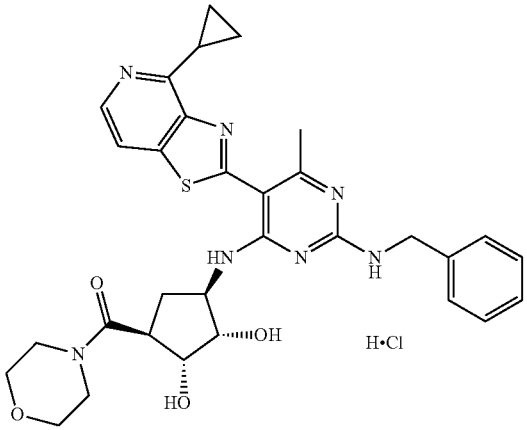
Compd #	Structure
2565	
2566	
2567	

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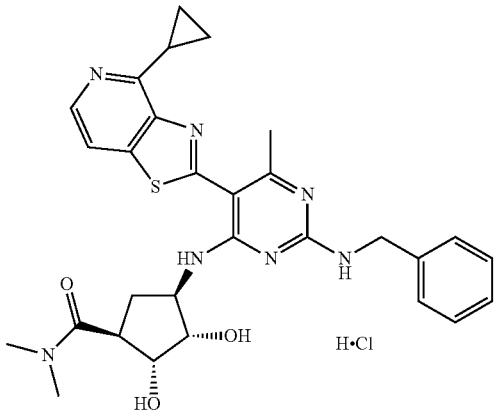
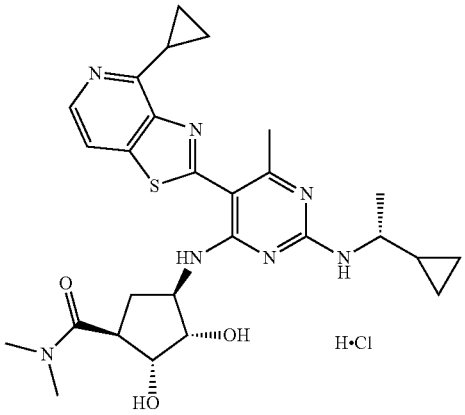
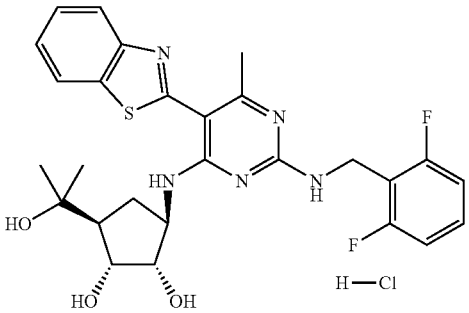
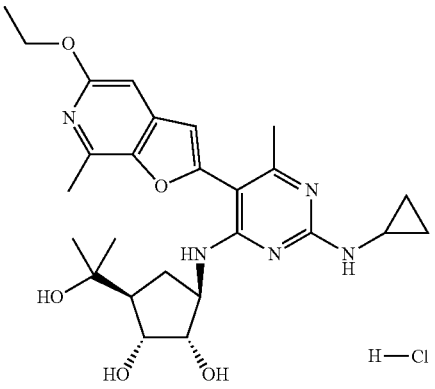
Compd #	Structure
2568	
2569	
2522	
2517	

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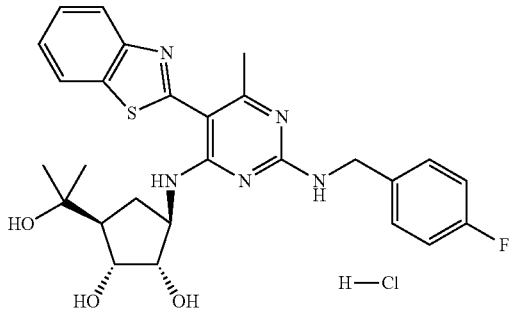
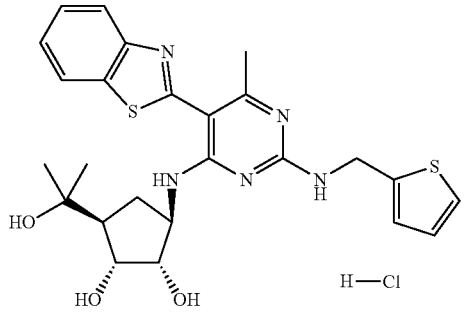
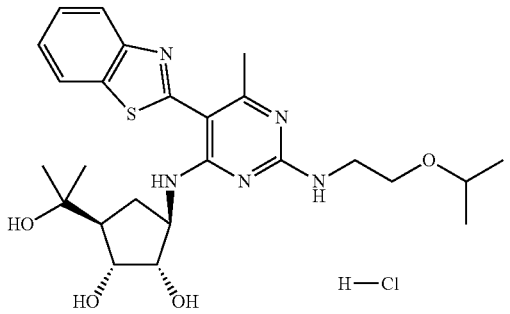
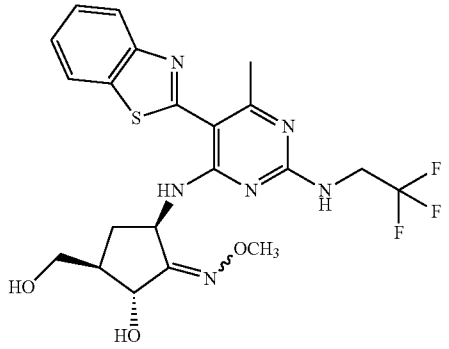
Compd #	Structure
2524	
2523	
2525	
2534	

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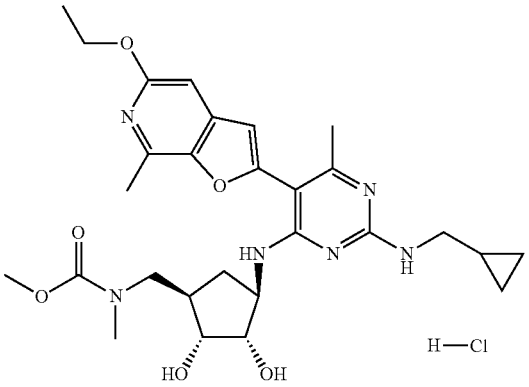
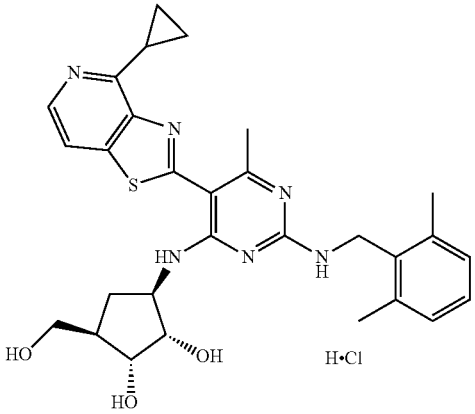
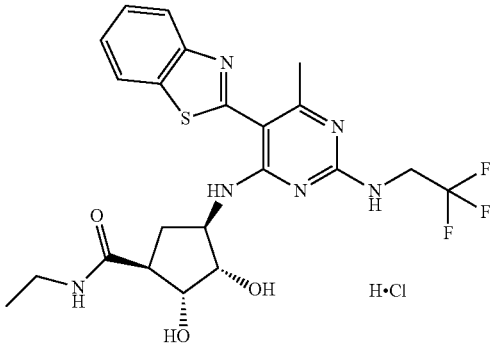
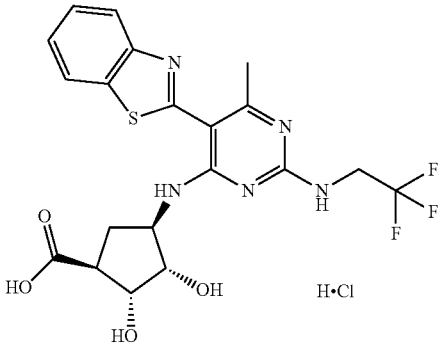
Compd #	Structure
2538	
2548	
2552	
2554	

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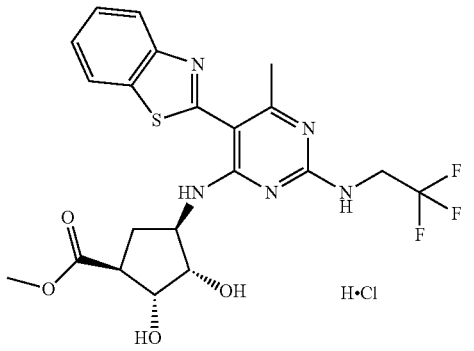
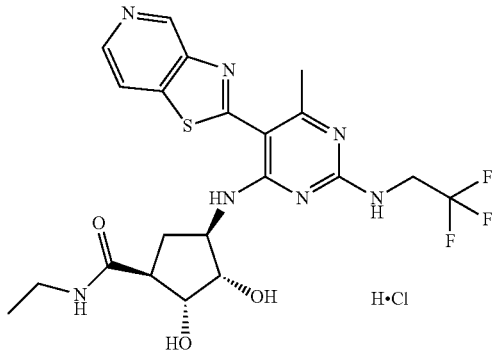
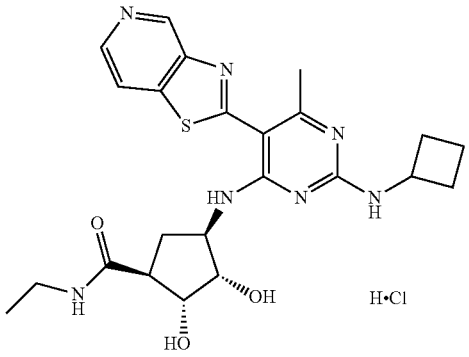
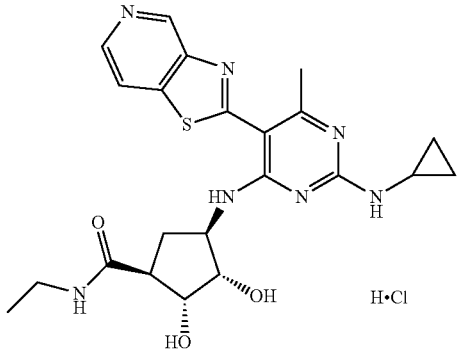
2557	
2558	
2560	
2561	

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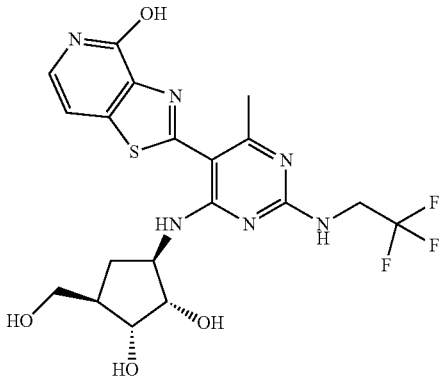
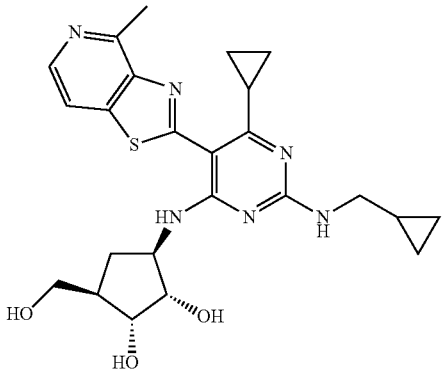
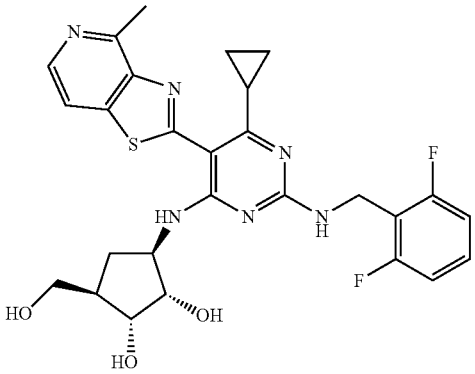
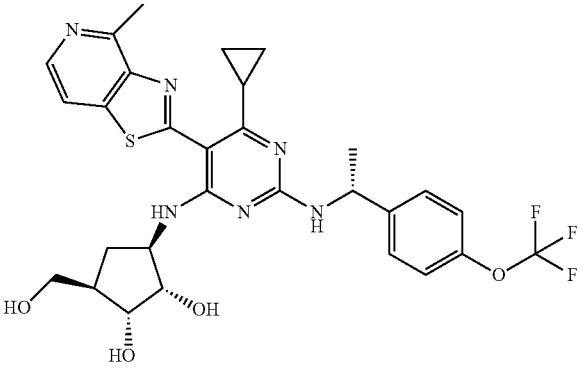
2501	
2529	
2528	
2530	

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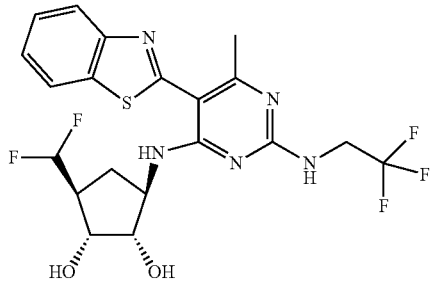
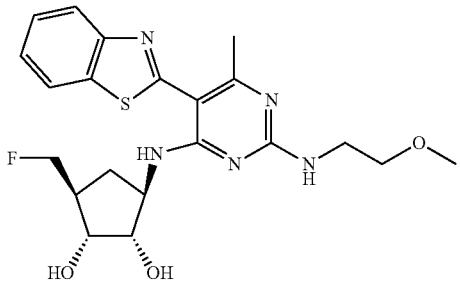
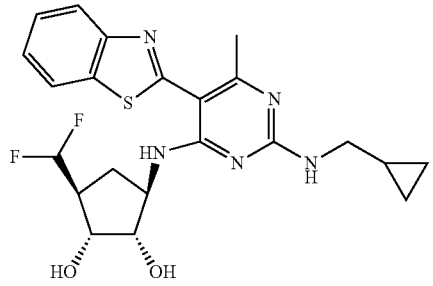
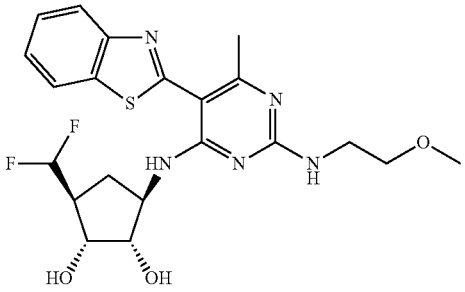
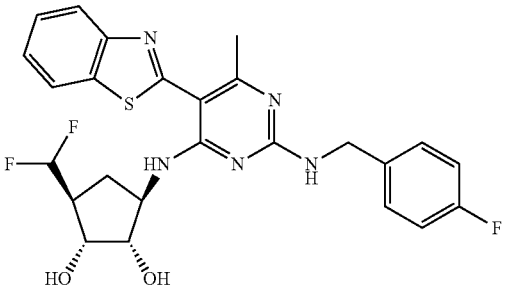
Compd #	Structure
3001	
3006	
3007	
3011	
3013	

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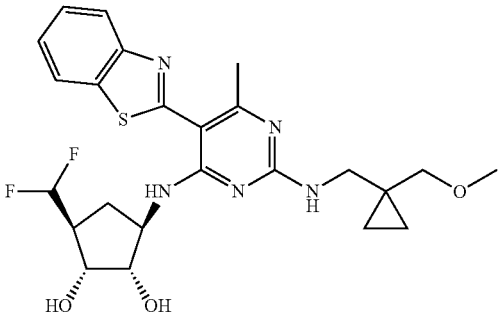
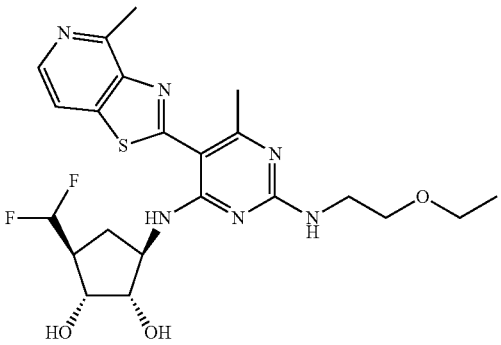
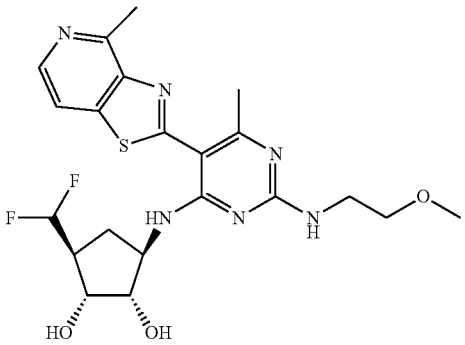
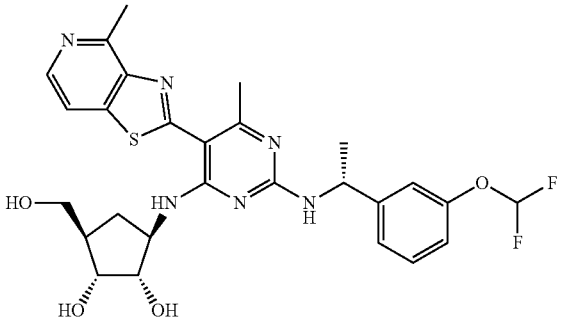
Compd #	Structure
3016	
3017	
3018	
3019	

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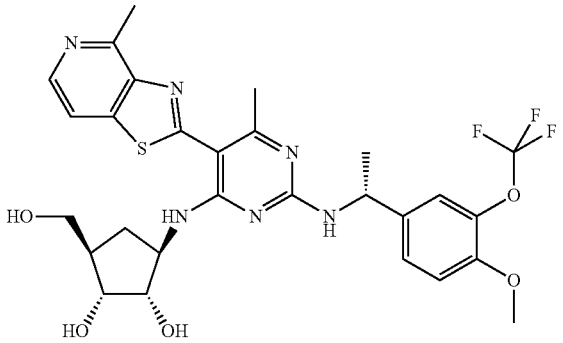
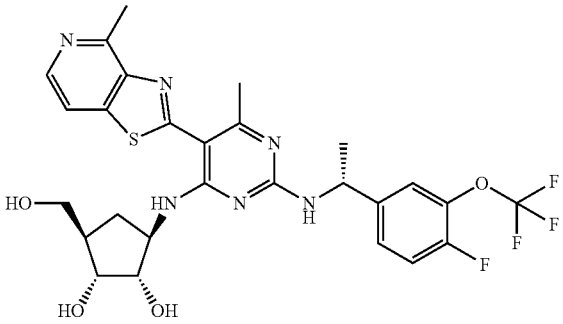
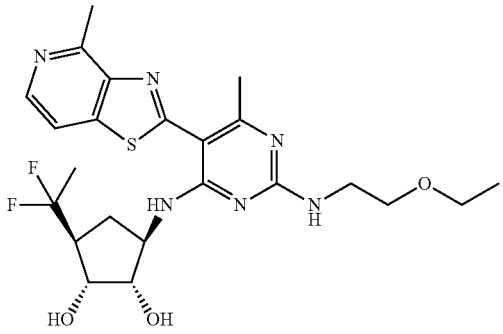
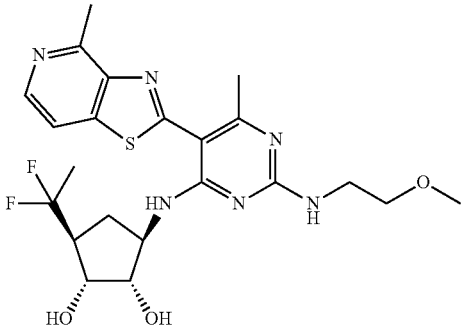
Compd #	Structure
3020	
3021	
3022	
3023	

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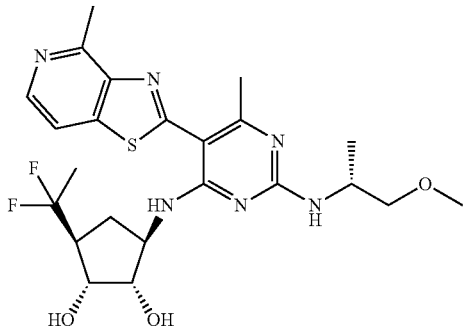
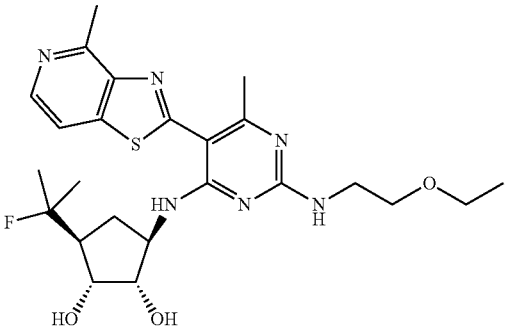
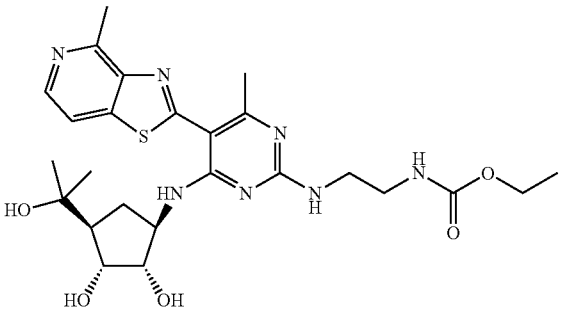
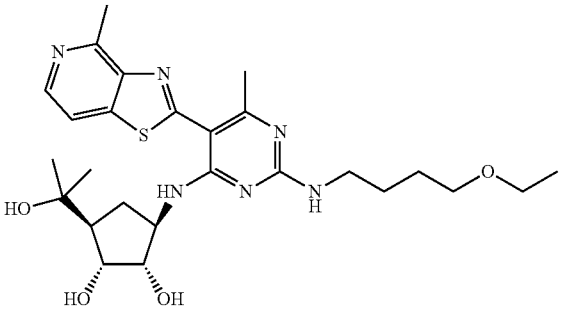
Compd #	Structure
3024	
3025	
3026	
3028	

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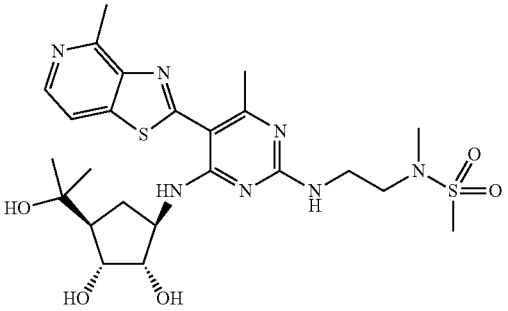
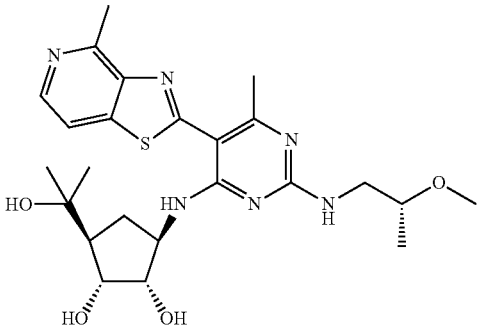
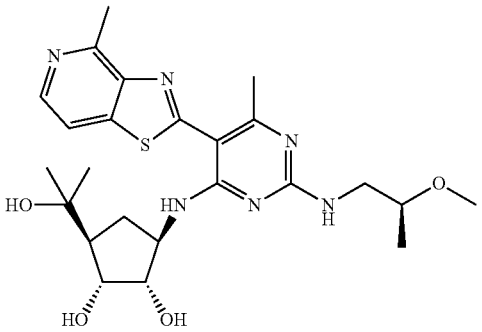
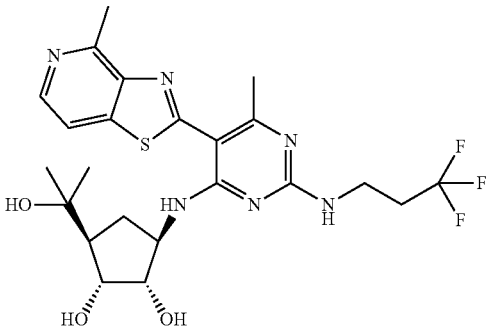
3029	
3030	
3031	
3032	

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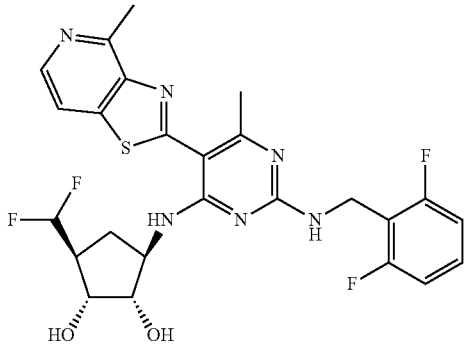
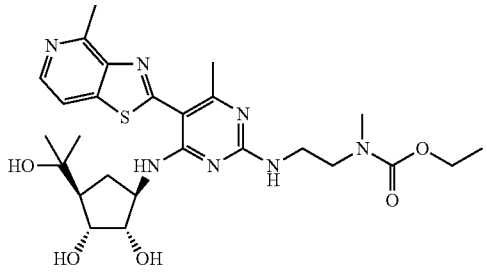
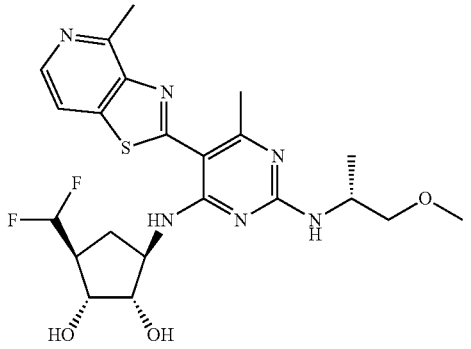
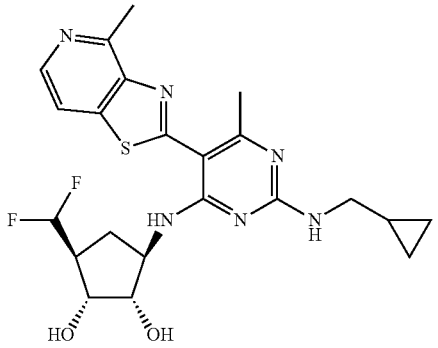
Compd #	Structure
3033	
3034	
3035	
3036	

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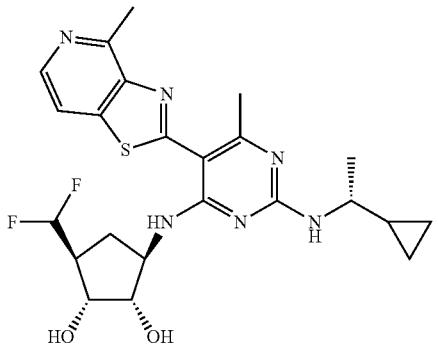
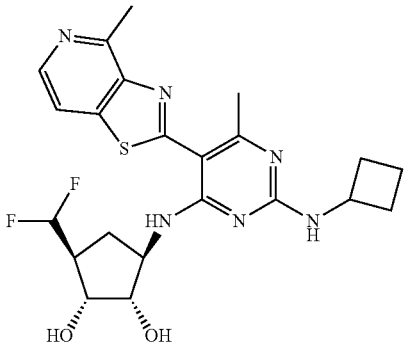
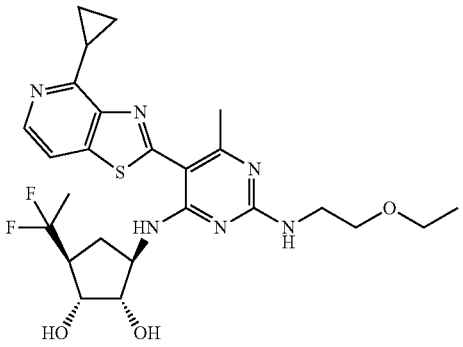
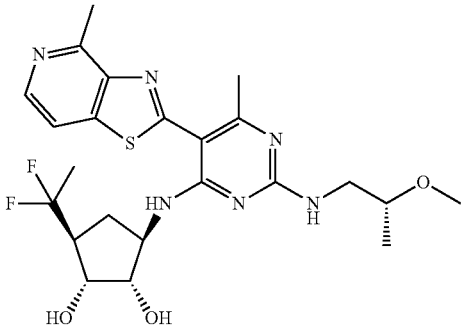
Compd #	Structure
3037	
3038	
3039	
3040	

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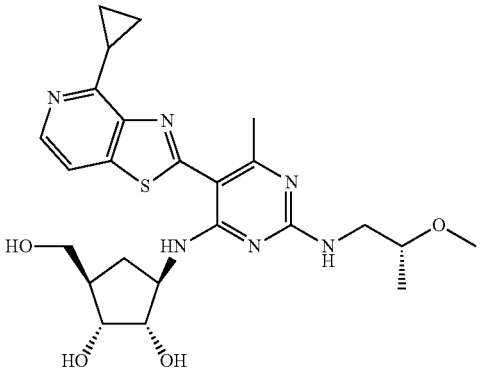
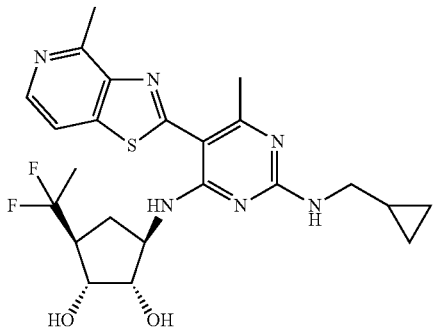
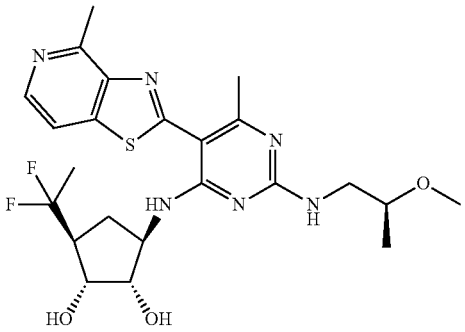
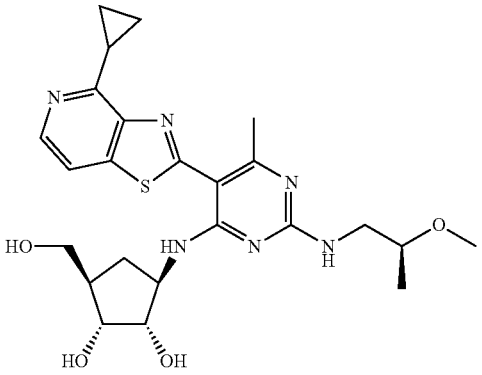
3041	
3042	
3043	
3044	

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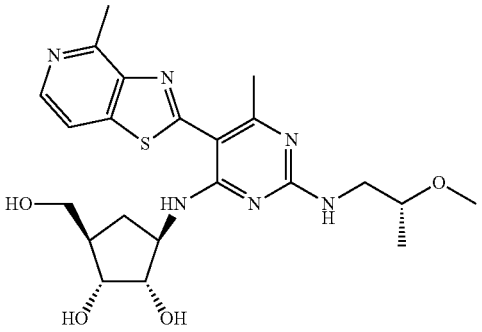
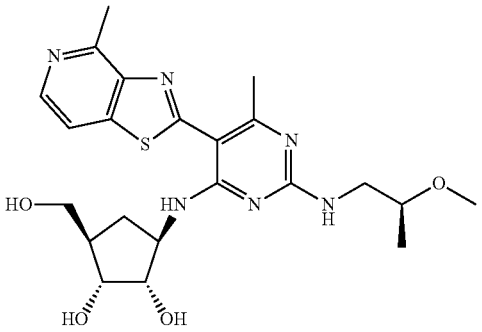
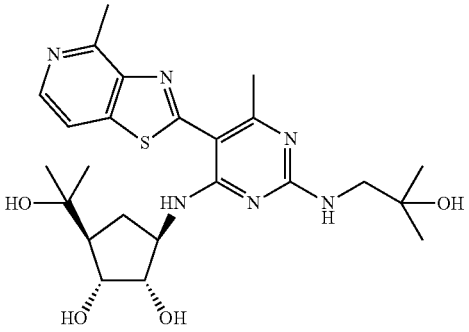
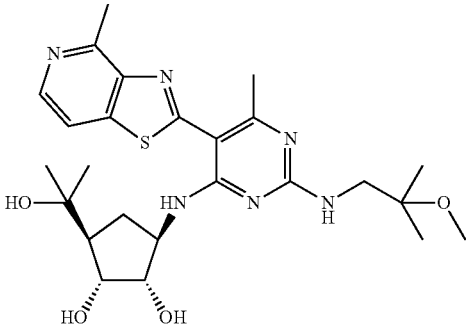
3045	
3046	
3047	
3048	

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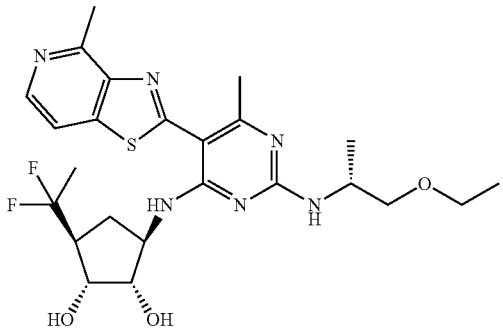
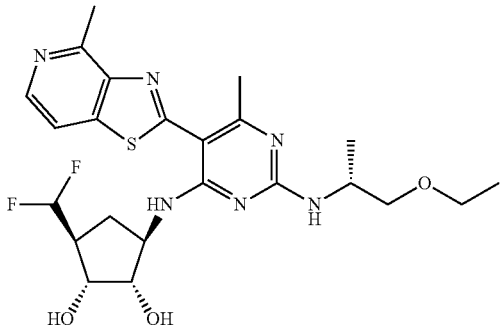
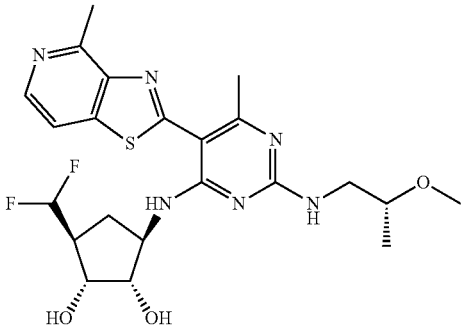
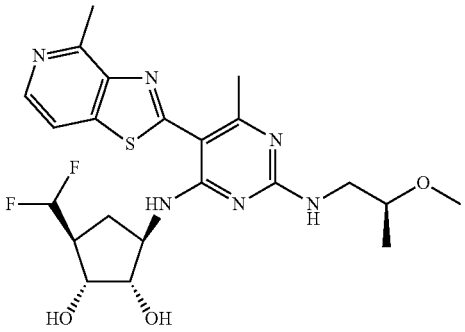
Compd #	Structure
3049	
3050	
3051	
3052	

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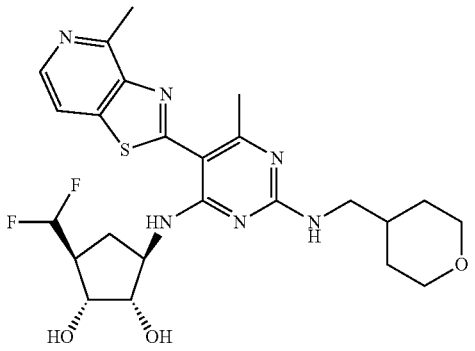
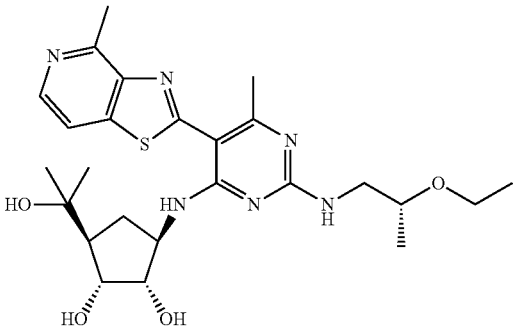
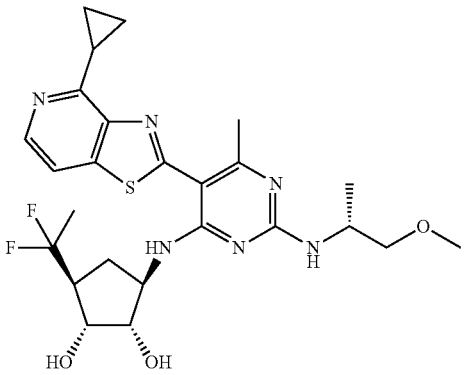
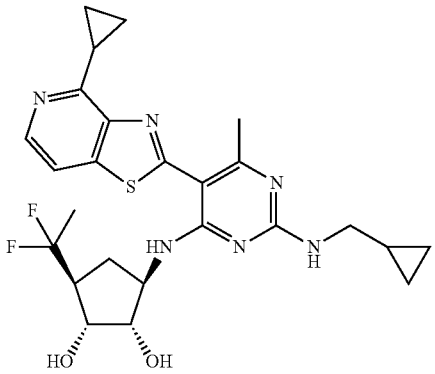
3053	
3054	
3055	
3056	

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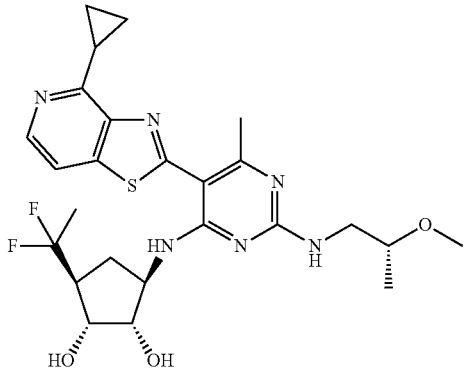
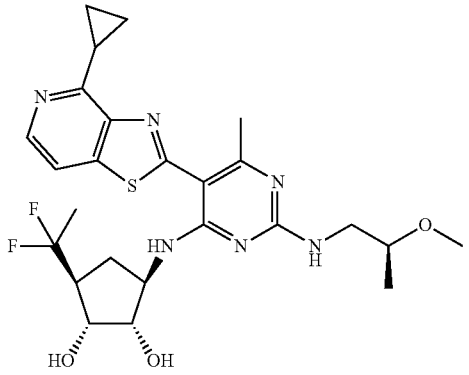
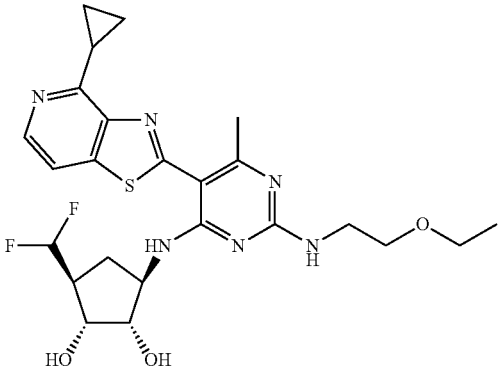
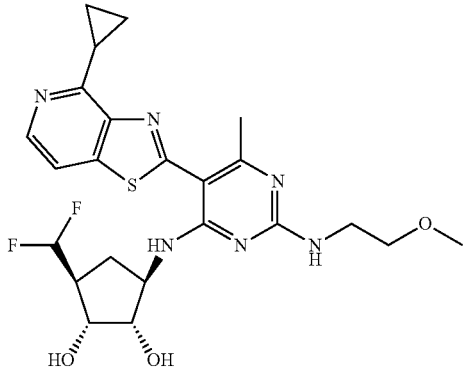
3057	
3058	
3059	
3060	

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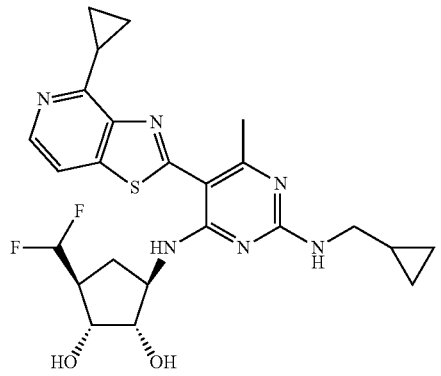
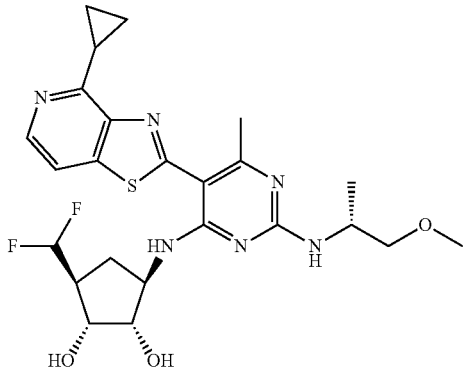
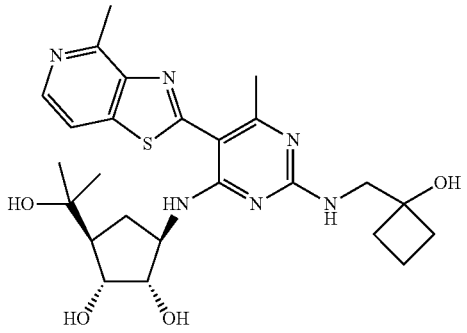
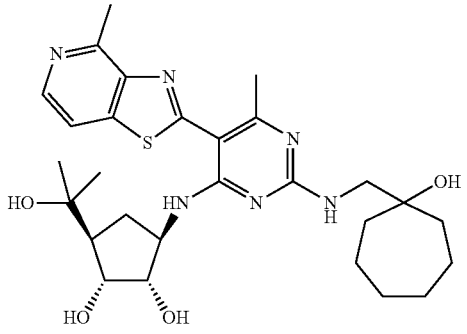
3061	
3062	
3063	
3064	

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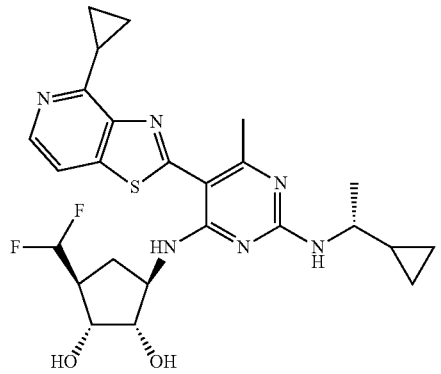
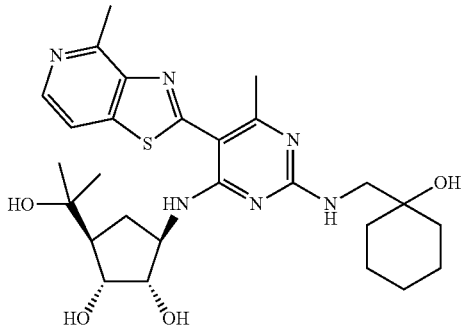
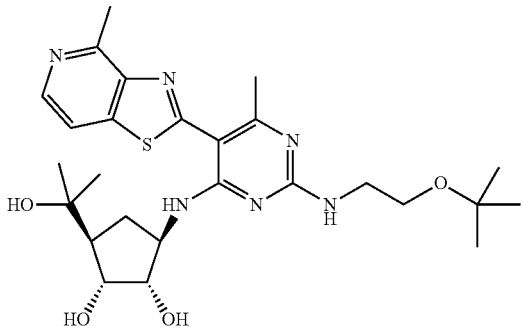
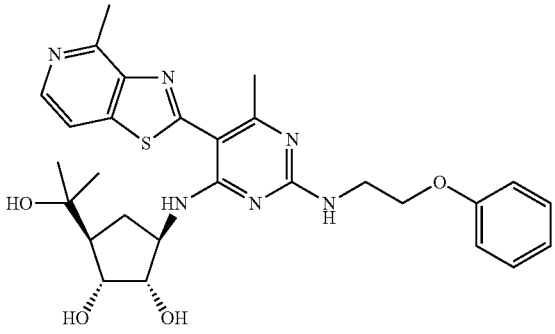
Compd #	Structure
3065	
3066	
3067	
3068	

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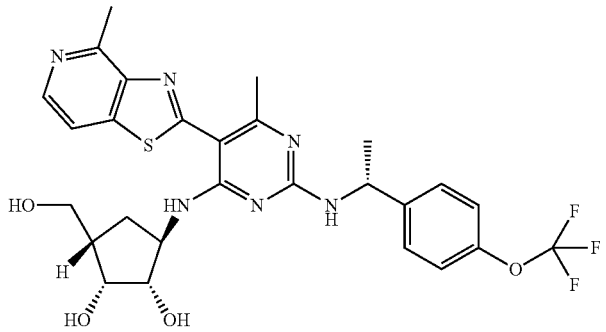
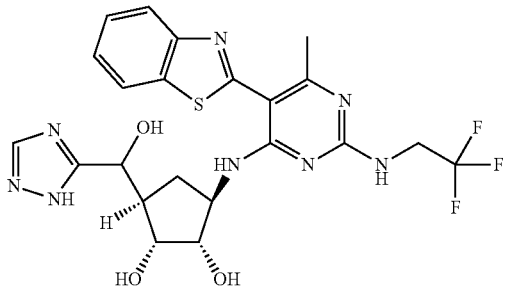
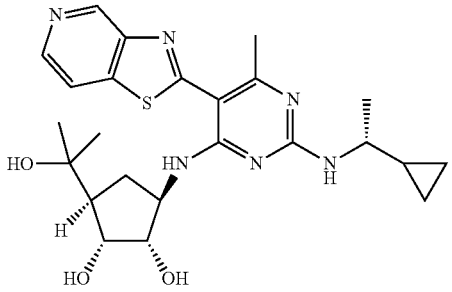
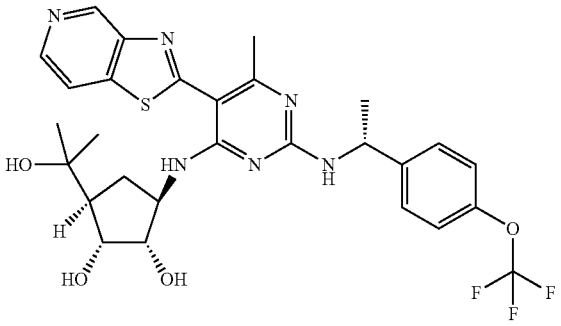
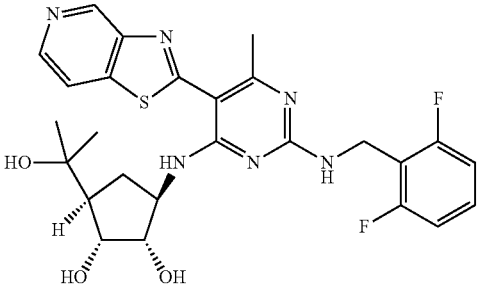
Compd #	Structure
3104	
3105	
3106	
3107	
3108	

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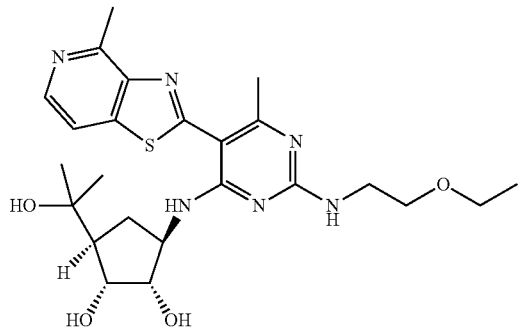
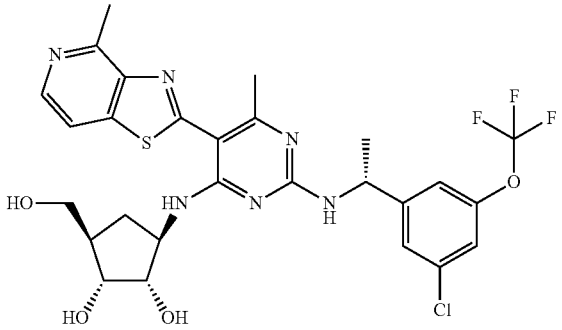
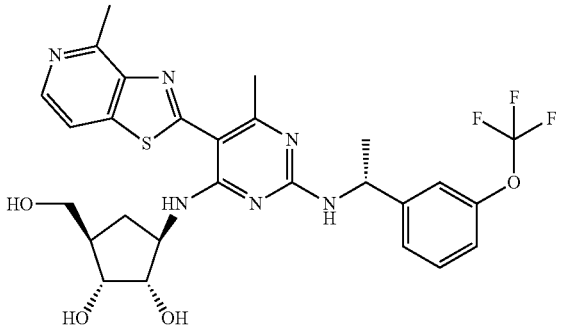
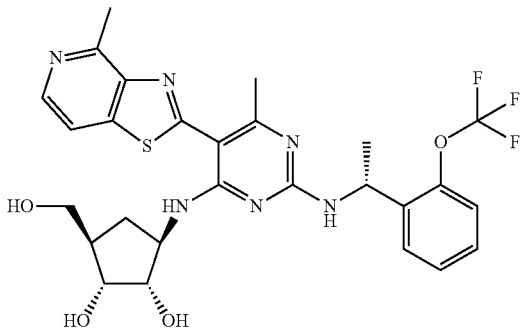
Compd #	Structure
3109	
3111	
3112	
3113	

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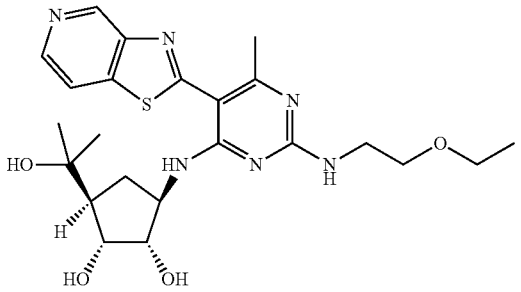
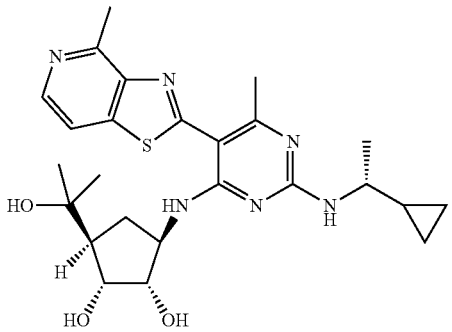
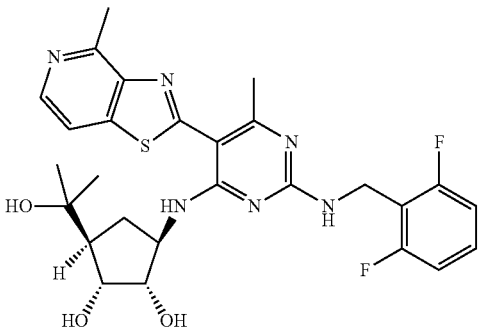
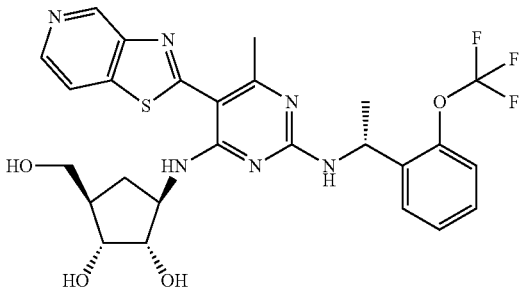
Compd #	Structure
3114	
3115	
3116	
3117	

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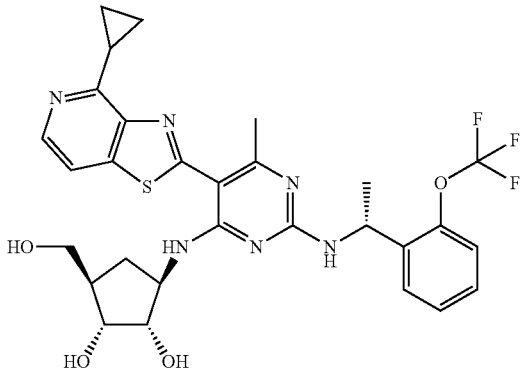
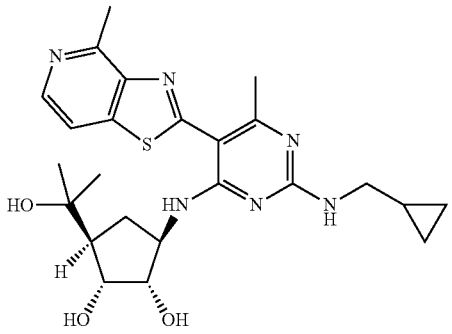
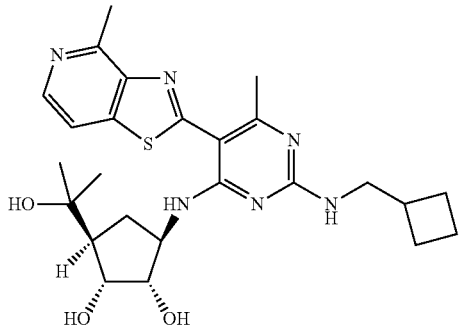
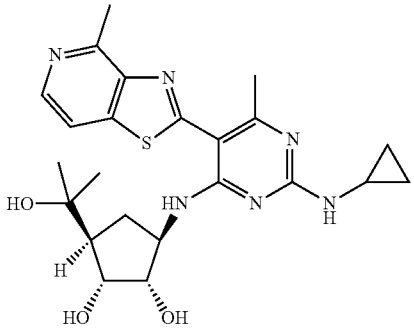
Compd #	Structure
3118	
3119	
3120	
3121	

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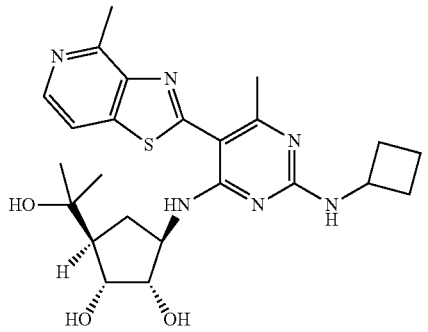
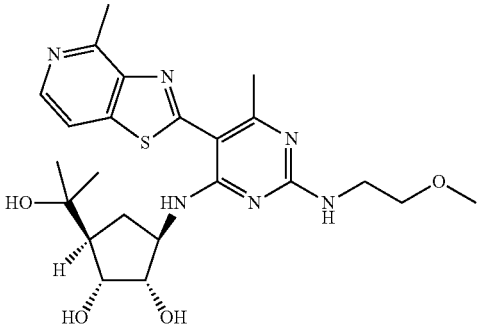
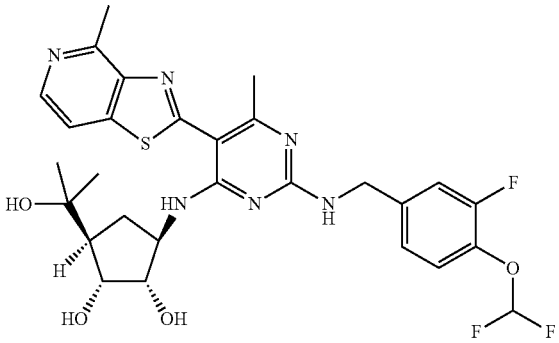
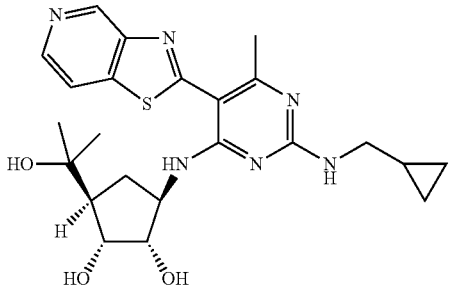
Compd #	Structure
3122	
3123	
3125	
3126	

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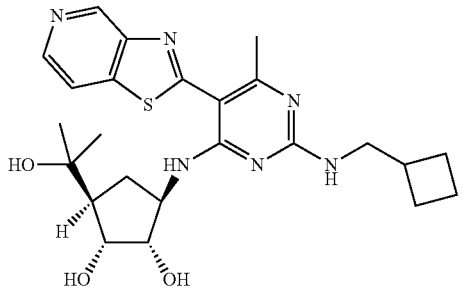
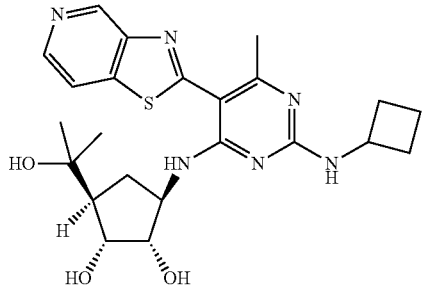
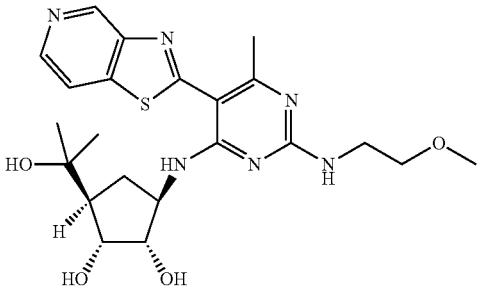
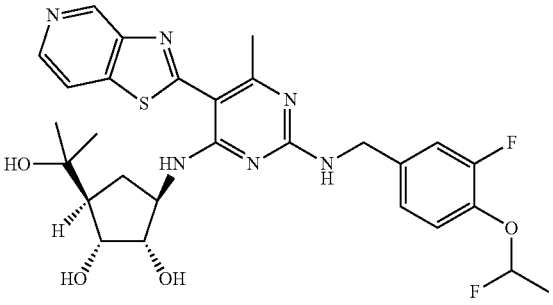
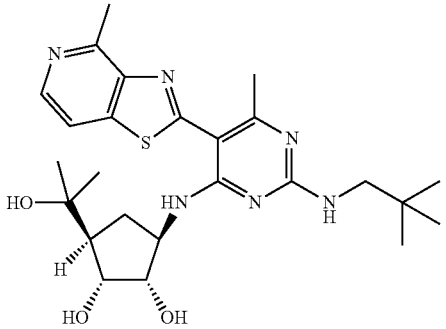
Compd #	Structure
3127	
3129	
3130	
3132	
3133	

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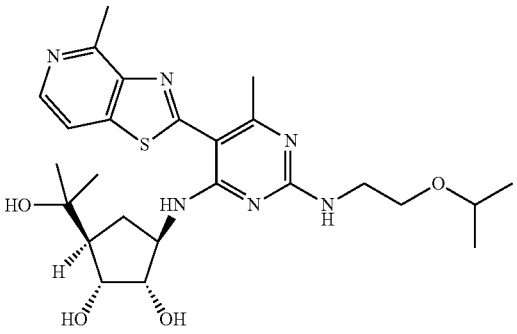
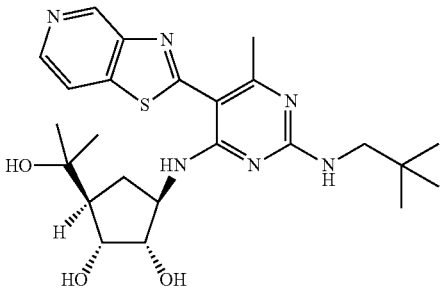
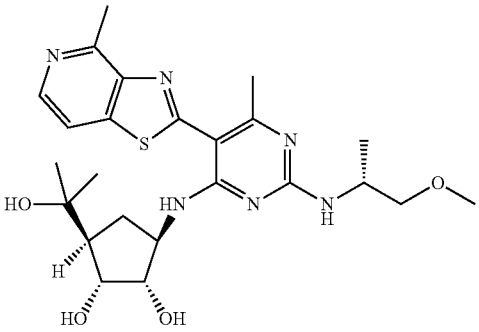
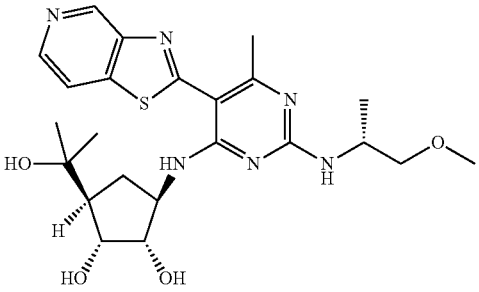
Compd #	Structure
3135	
3136	
3137	
3138	

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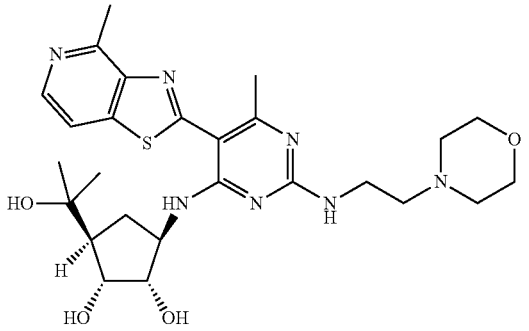
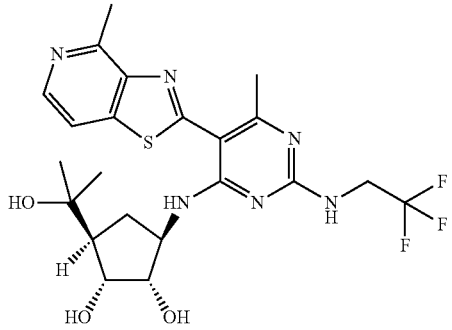
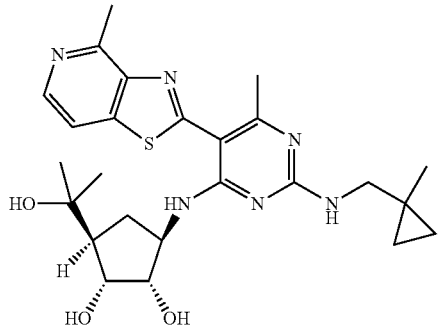
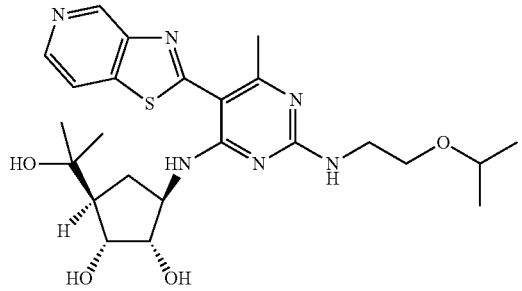
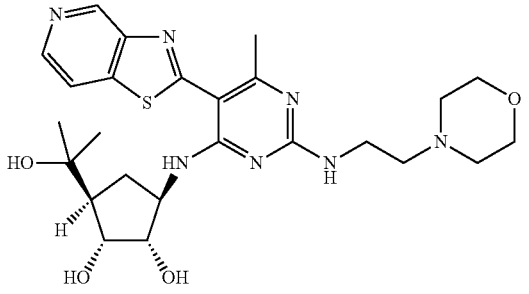
3139	
3141	
3142	
3144	
3145	

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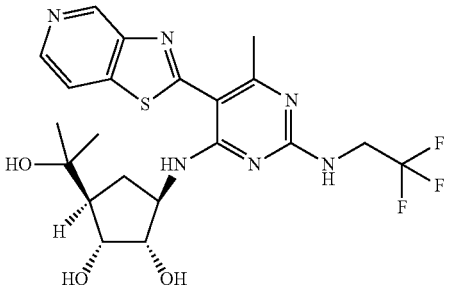
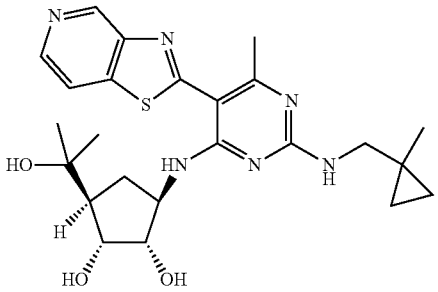
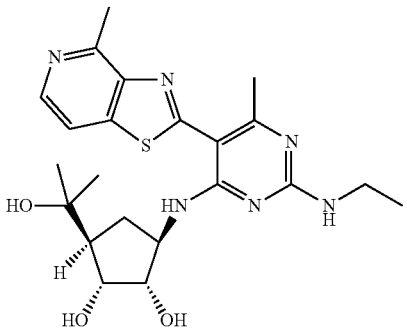
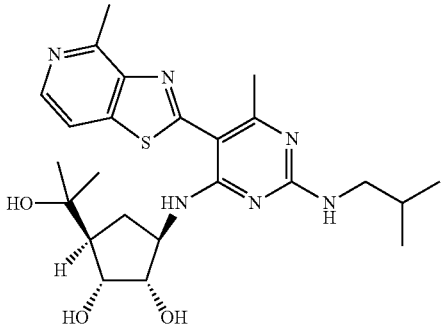
Compd #	Structure
3146	
3147	
3148	
3149	

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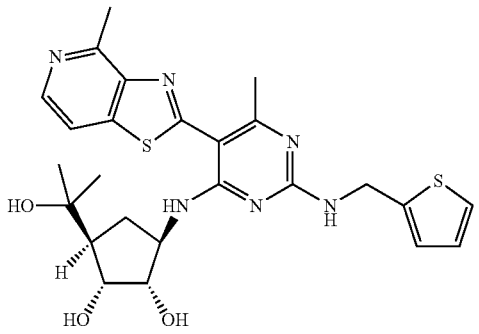
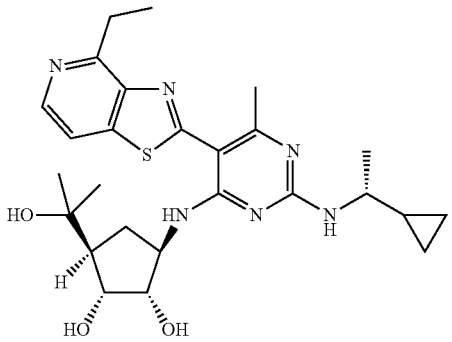
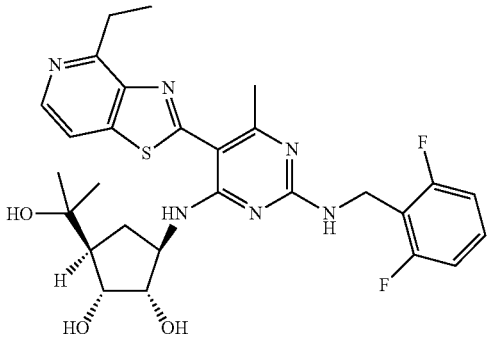
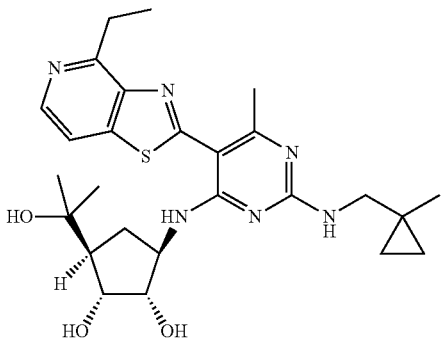
Compd #	Structure
3153	
3154	
3155	
3156	

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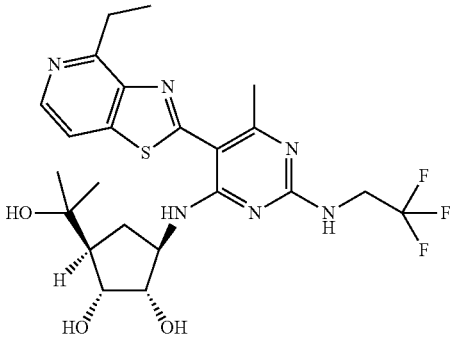
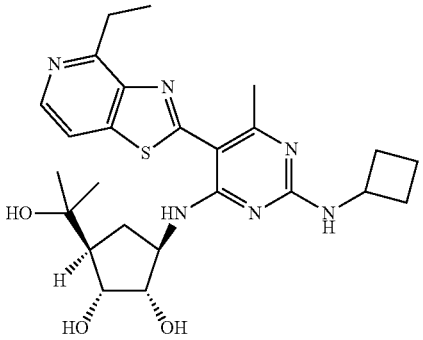
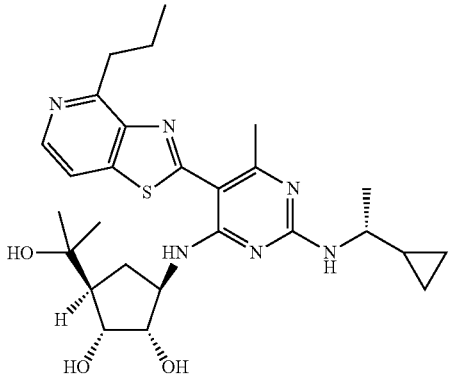
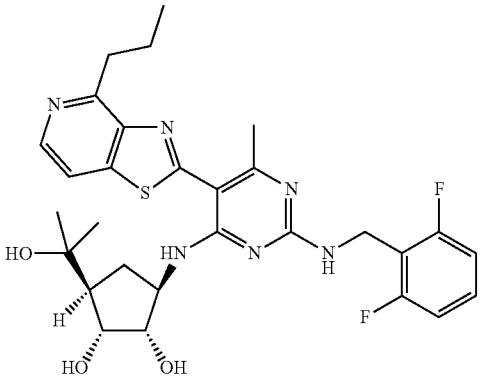
3157	
3158	
3159	
3160	

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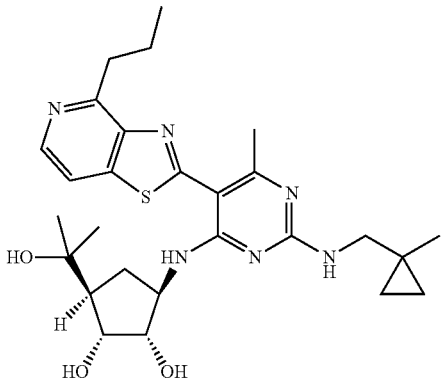
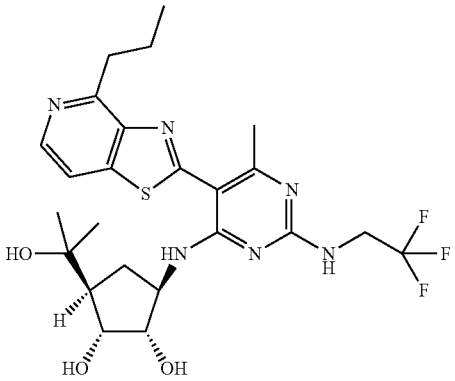
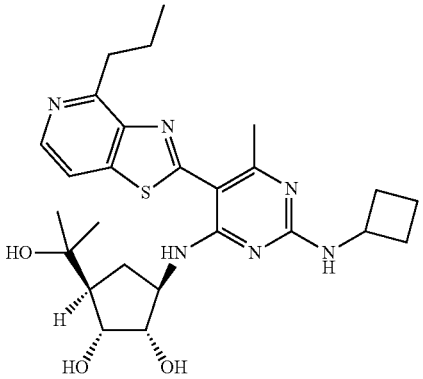
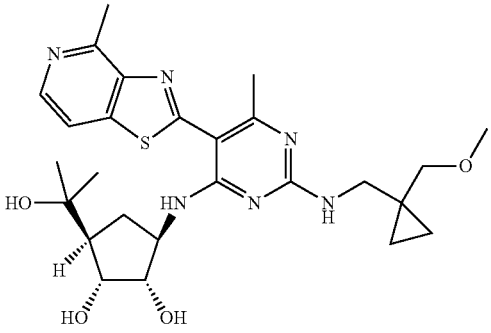
Compd #	Structure
3161	
3162	
3163	
3164	

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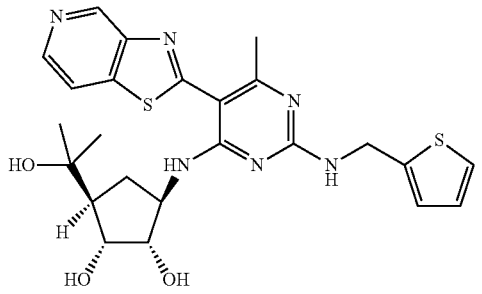
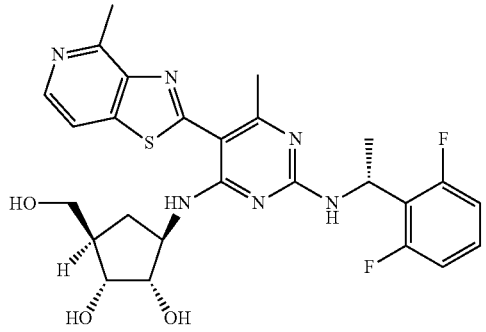
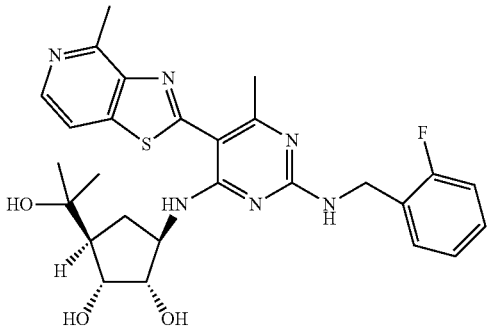
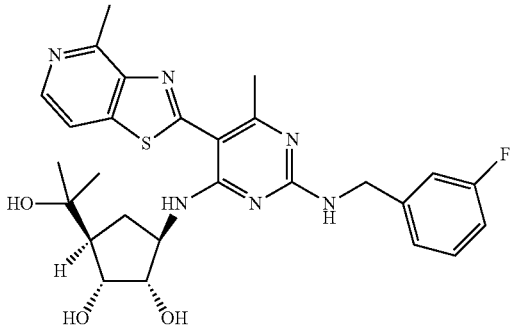
3165	
3166	
3167	
3168	

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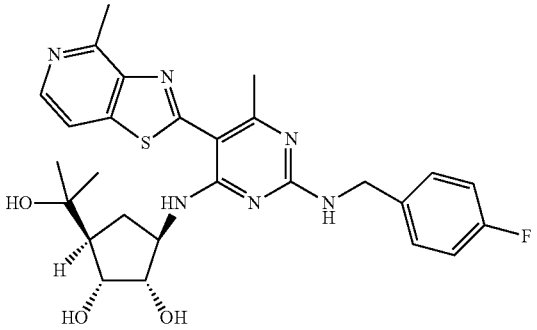
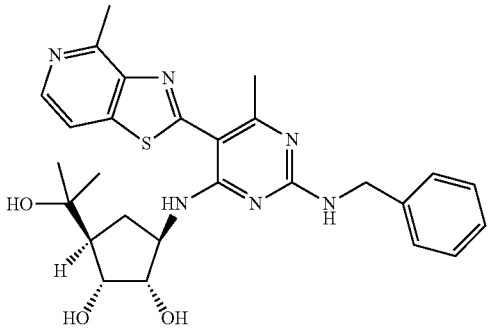
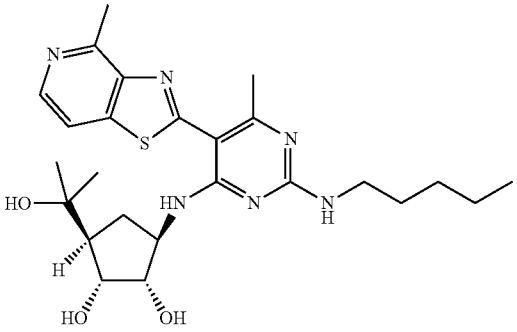
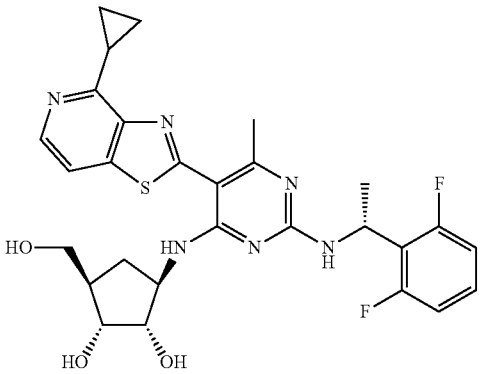
Compd #	Structure
3169	
3170	
3171	
3174	

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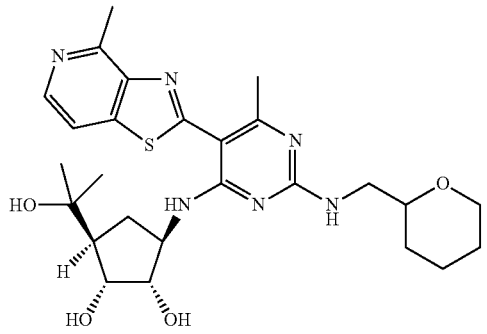
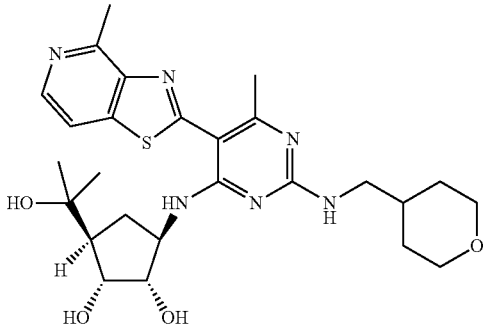
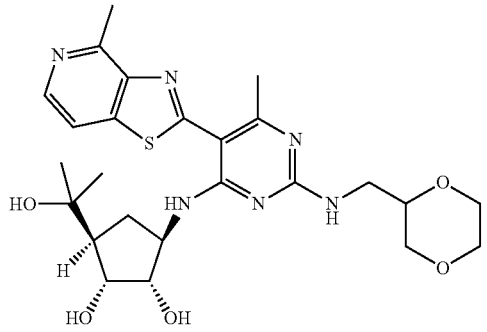
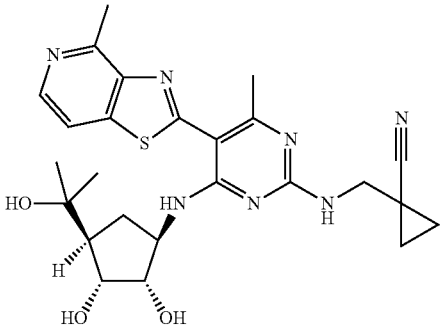
3175	
3176	
3177	
3178	

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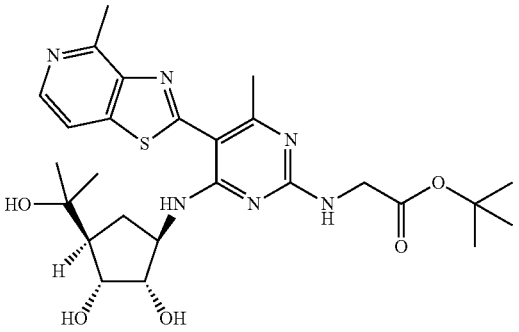
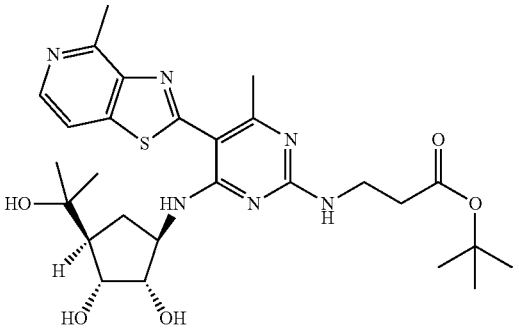
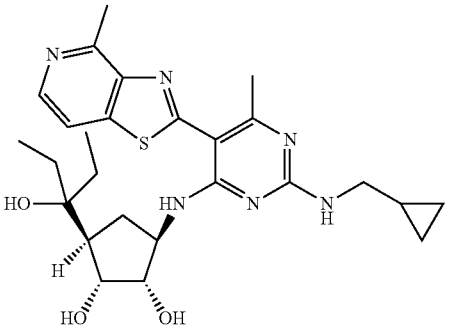
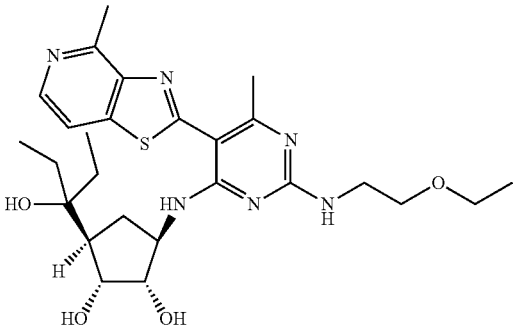
Compd #	Structure
3179	
3181	
3182	
3183	

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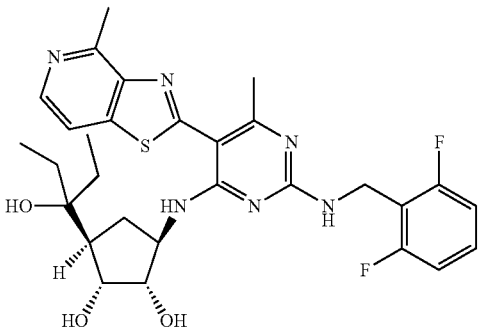
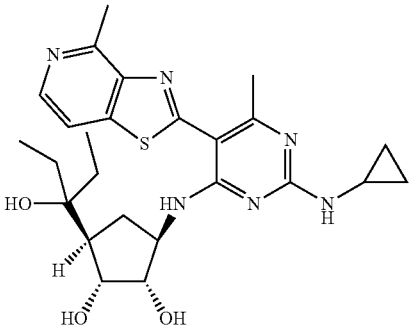
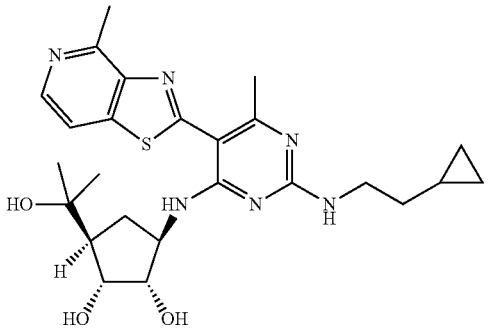
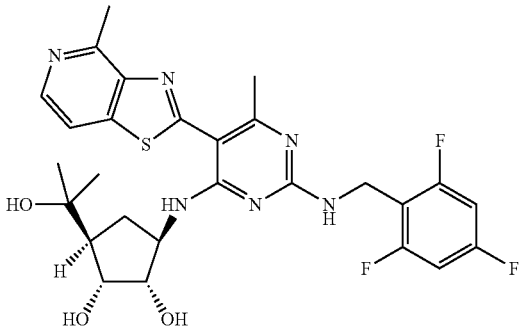
3185	
3186	
3187	
3188	

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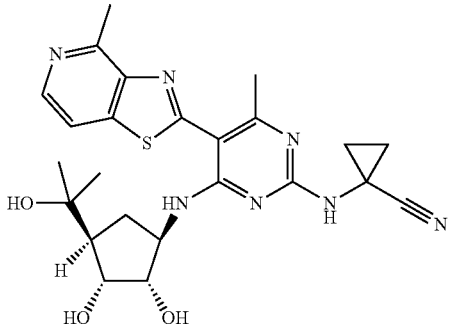
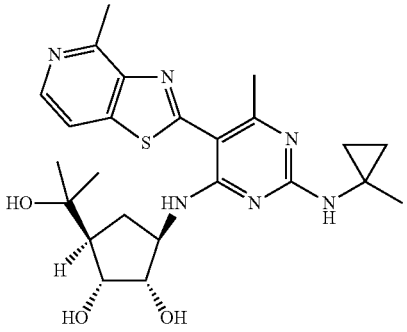
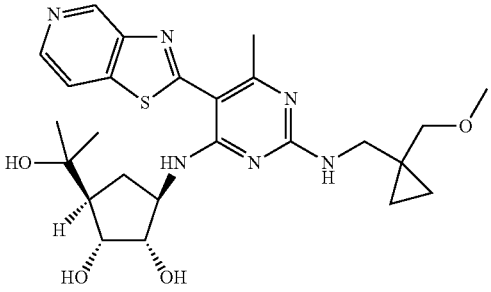
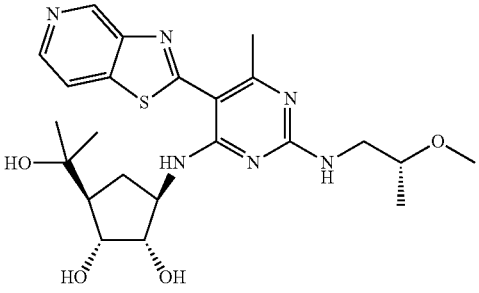
3189	
3190	
3191	
3192	

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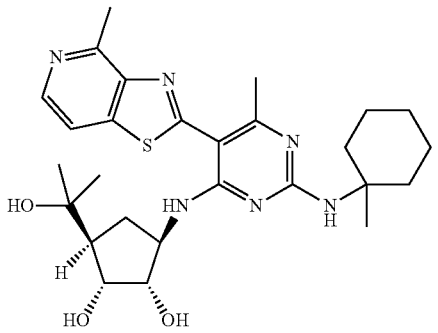
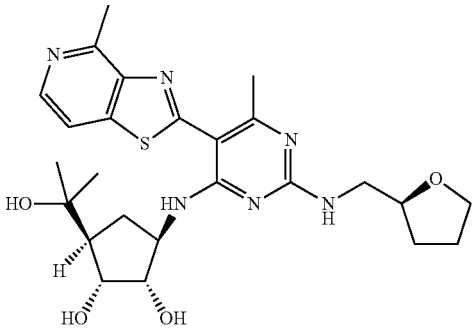
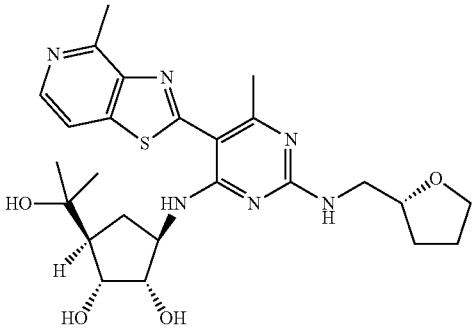
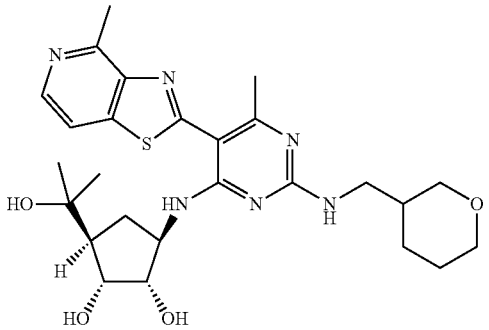
Compd #	Structure
3193	
3194	
3195	
3197	

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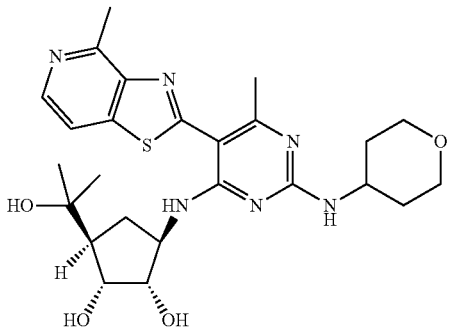
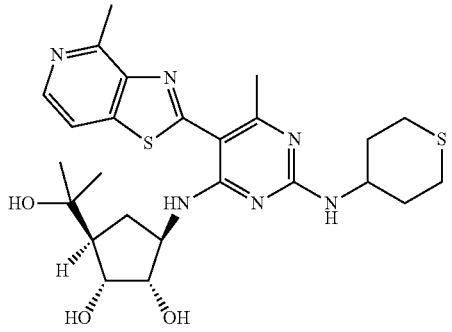
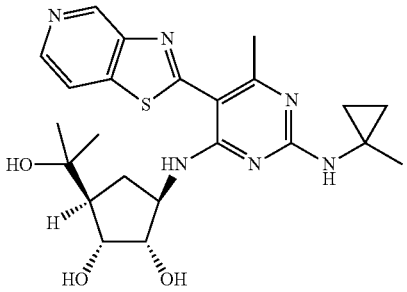
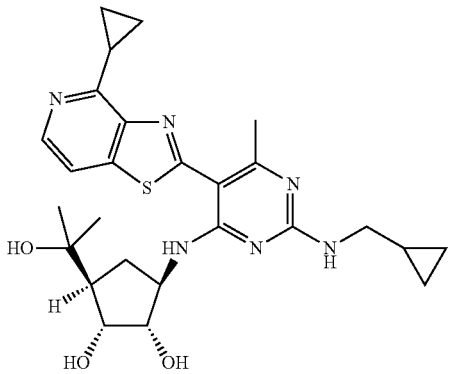
Compd #	Structure
3198	
3199	
3200	
3201	

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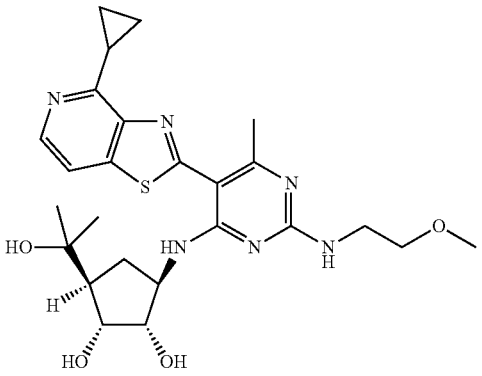
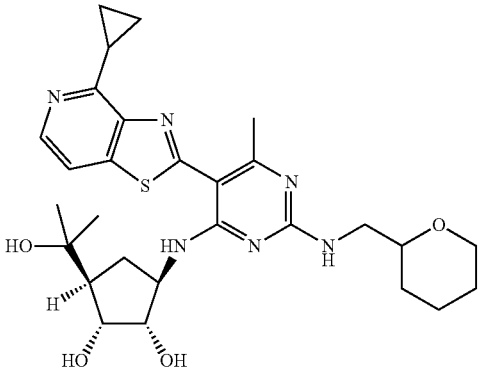
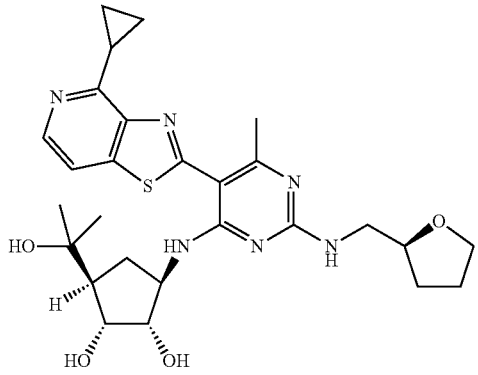
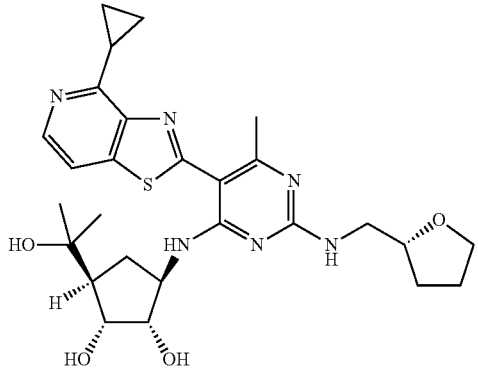
3202	
3204	
3205	
3206	

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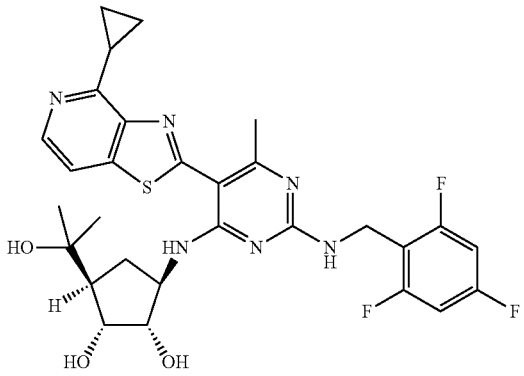
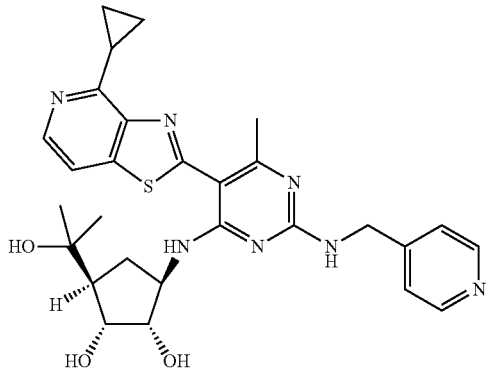
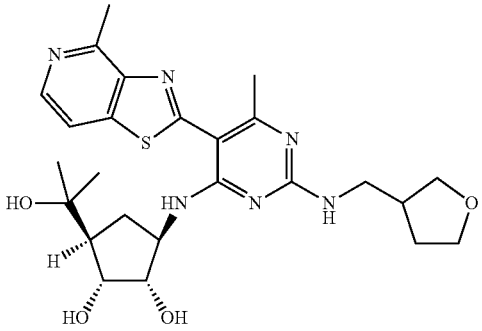
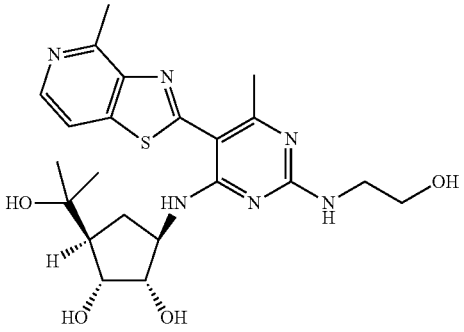
3207	
3208	
3209	
3210	

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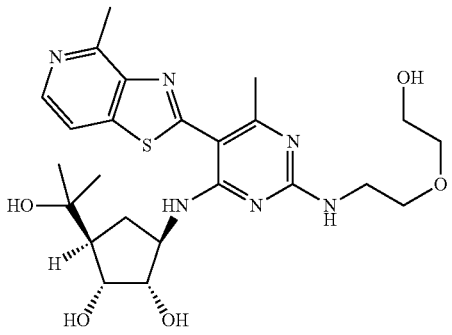
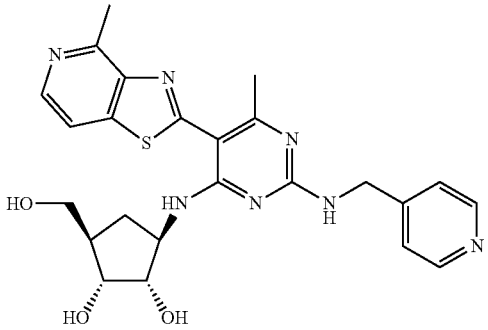
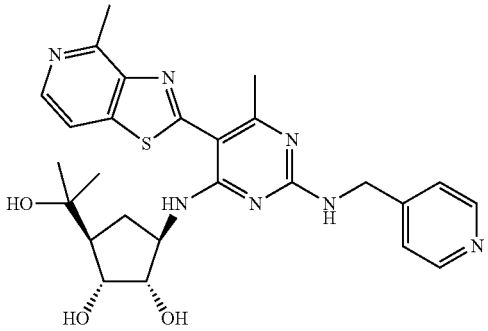
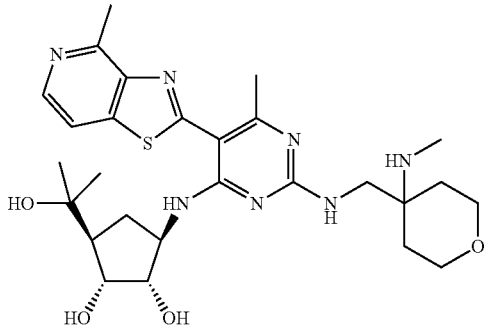
3211	
3212	
3213	
3214	

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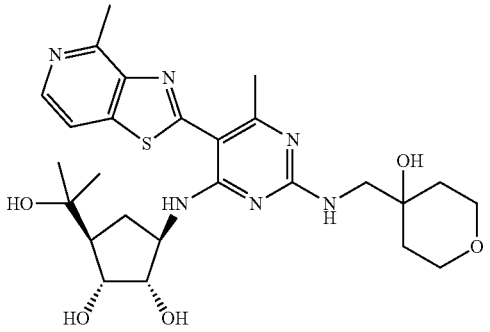
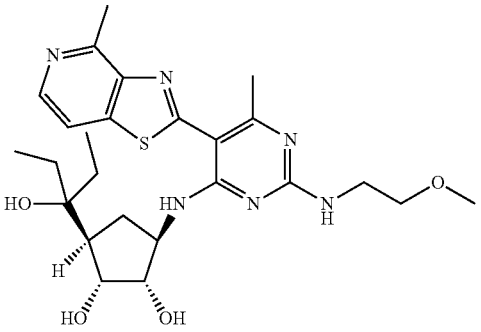
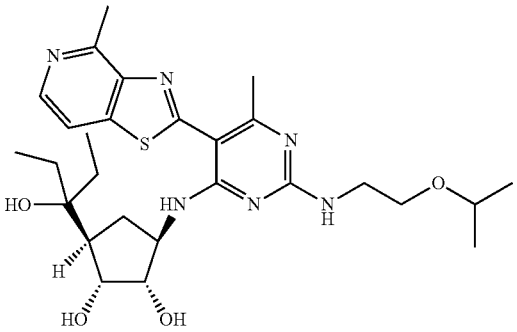
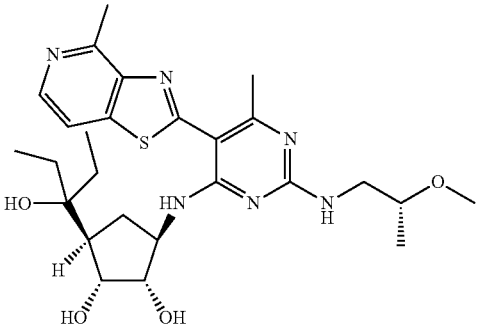
3215	
3216	
3217	
3218	

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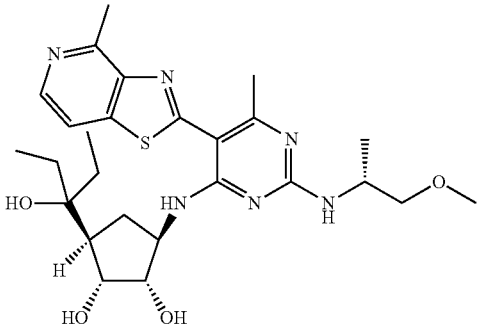
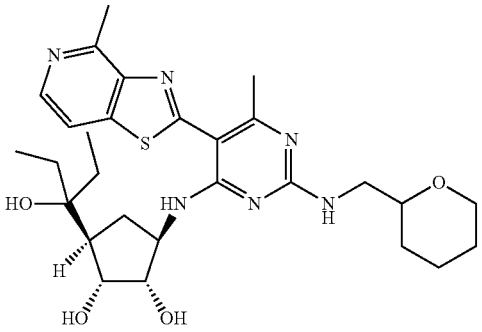
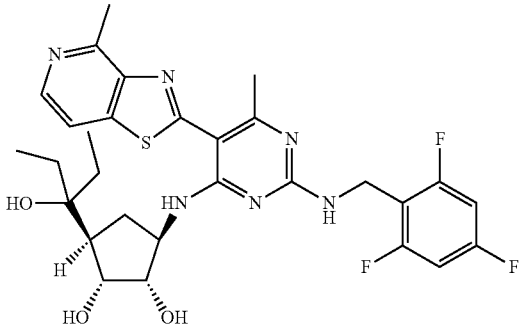
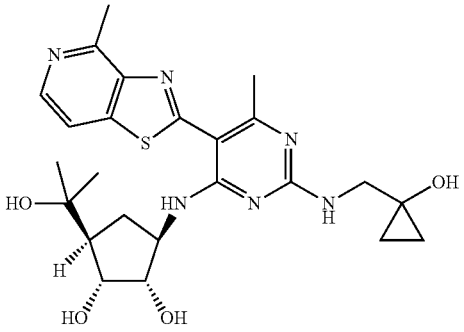
Compd #	Structure
3219	
3220	
3222	
3224	

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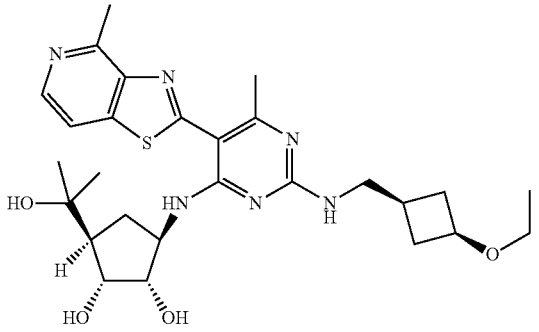
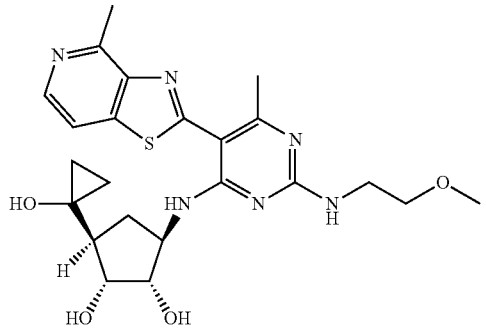
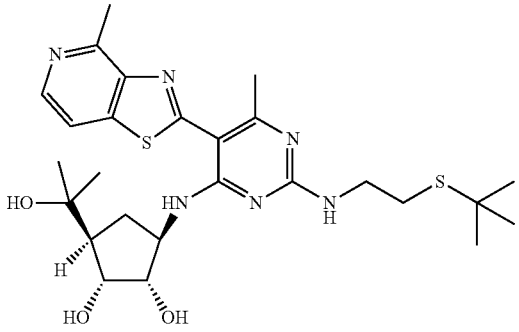
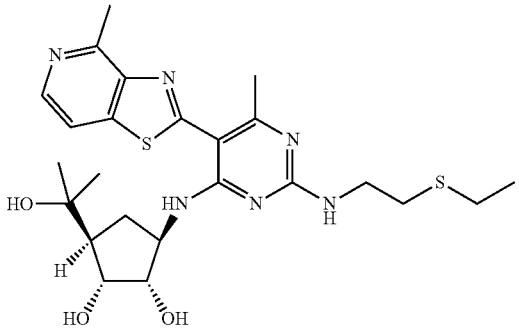
Compd #	Structure
3225	
3226	
3230	
3229	

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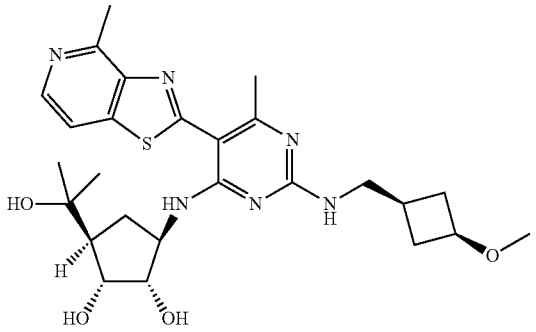
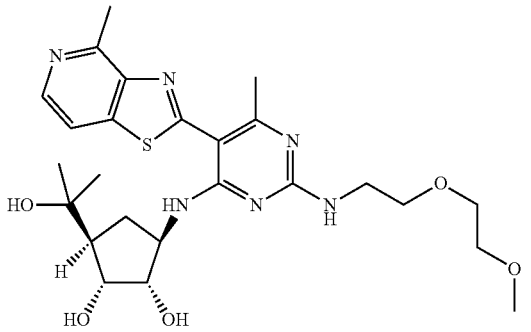
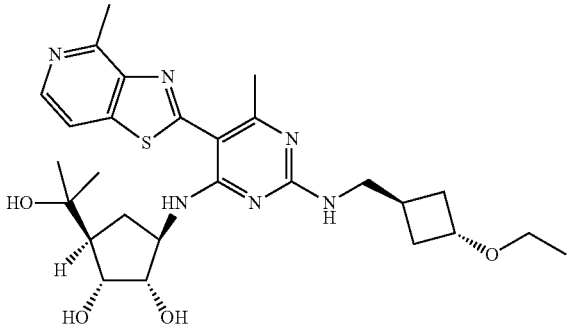
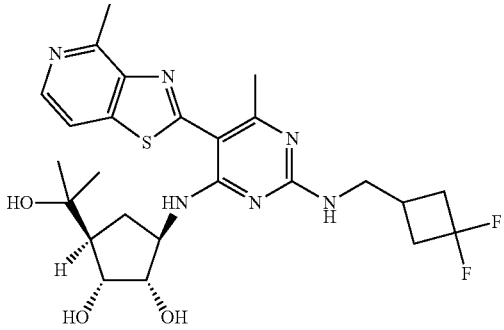
3233	
3231	
3240	
3239	

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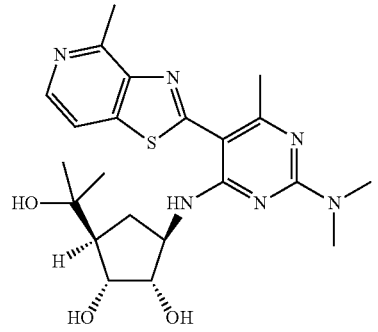
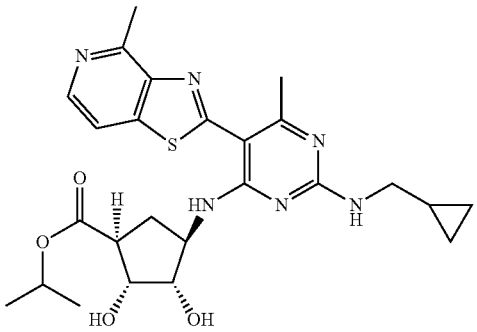
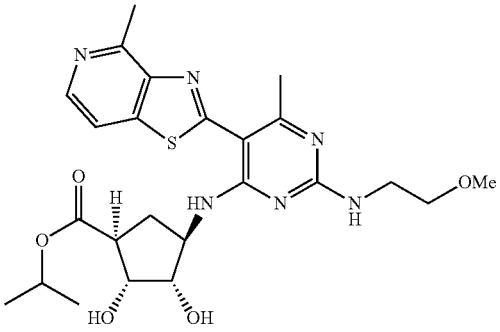
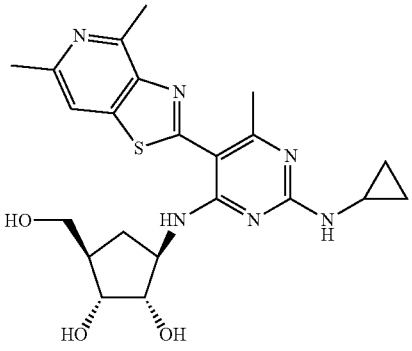
3241	
3242	
3243	
3301	

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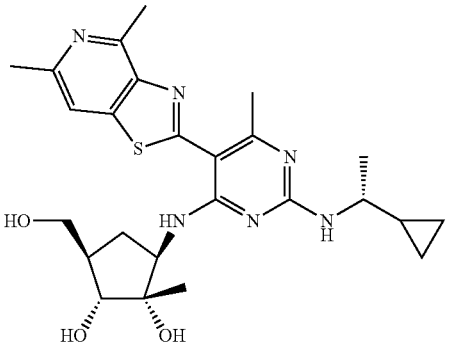
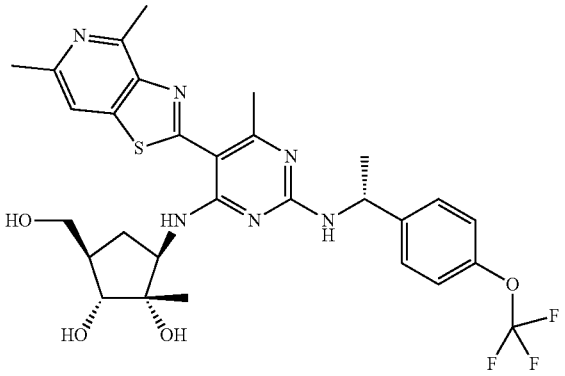
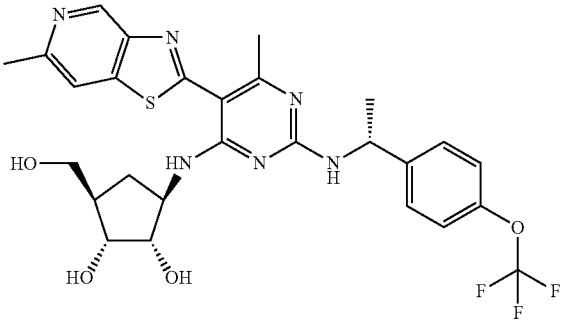
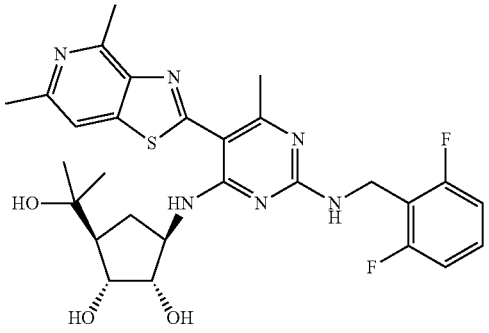
3302	
3303	
3304	
3305	

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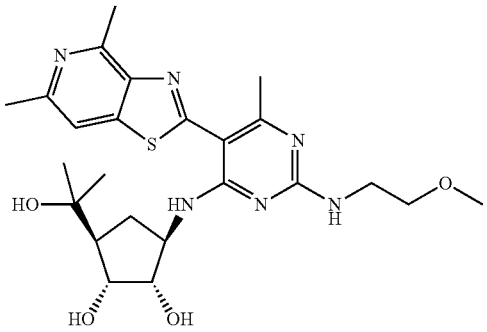
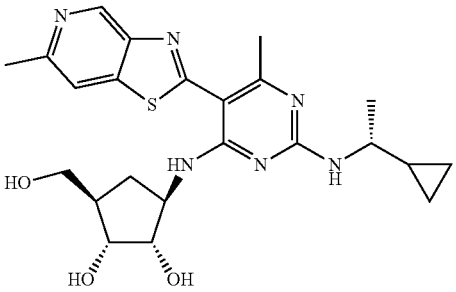
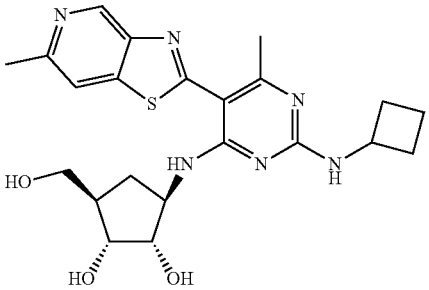
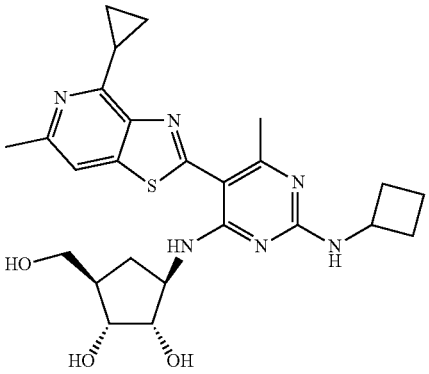
3306	
3307	
3308	
3309	

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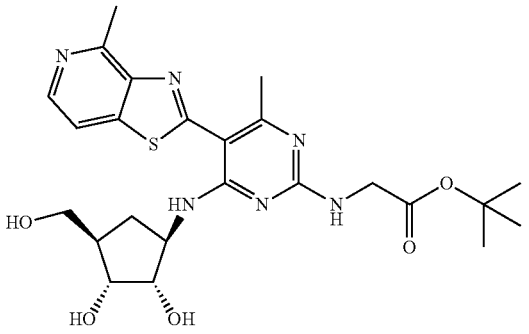
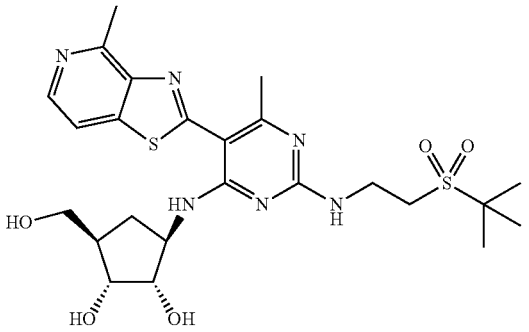
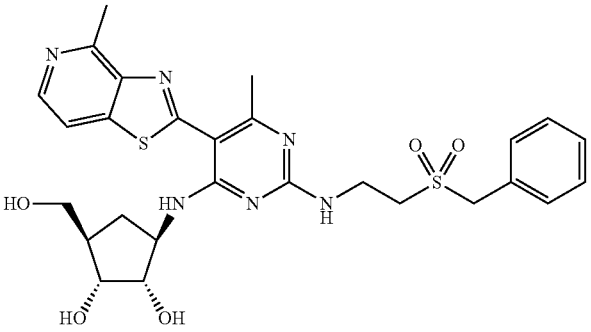
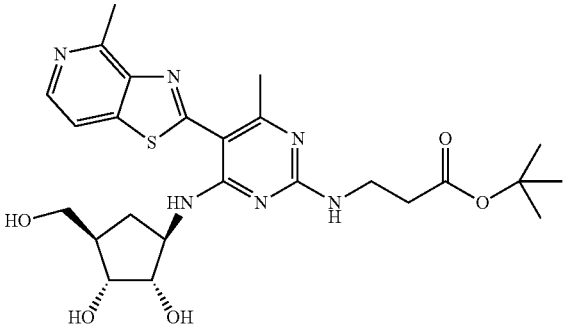
3310	
3313	
3314	
3315	

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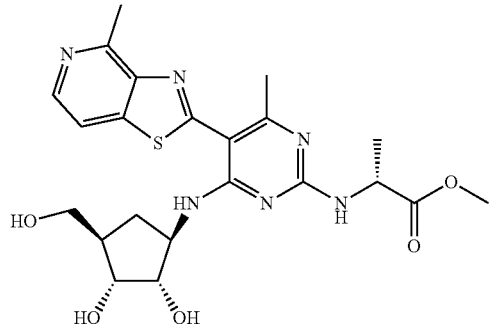
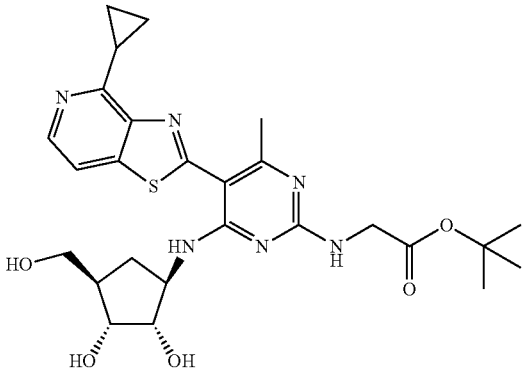
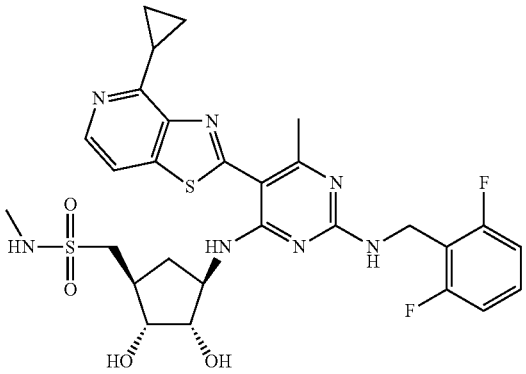
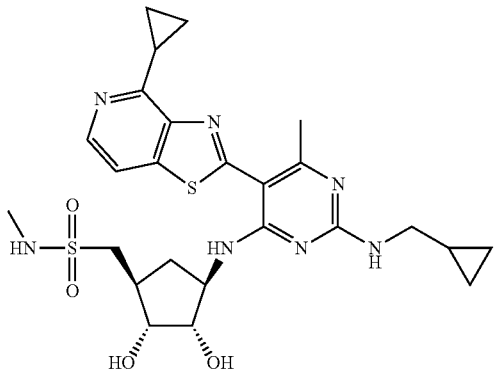
3316	
3317	
3318	
3319	

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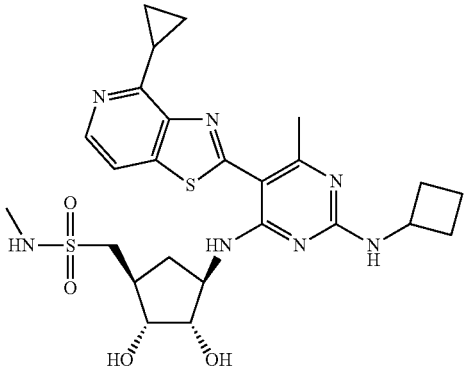
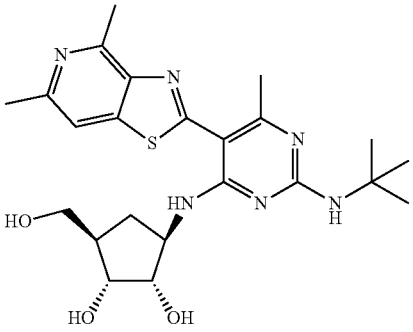
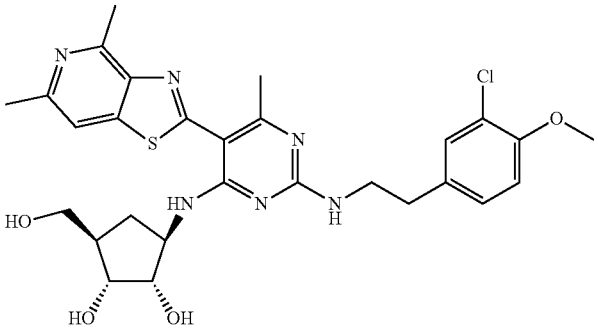
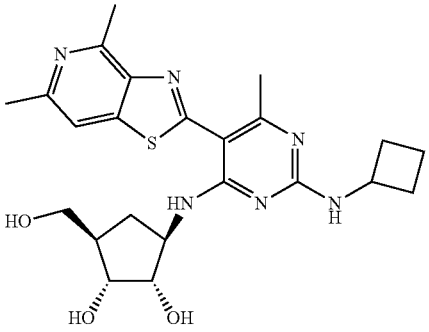
3320	
3401	
3402	
3405	

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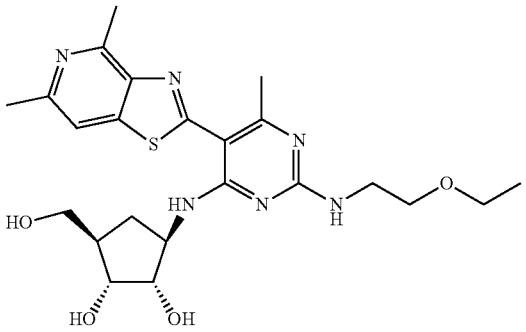
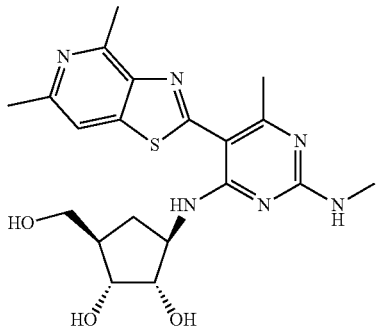
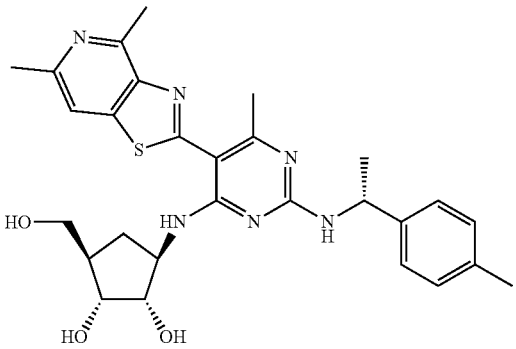
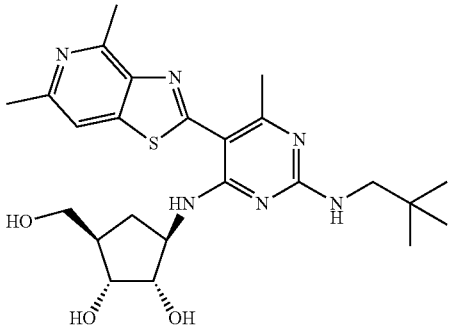
3408	
3411	
3412	
3415	

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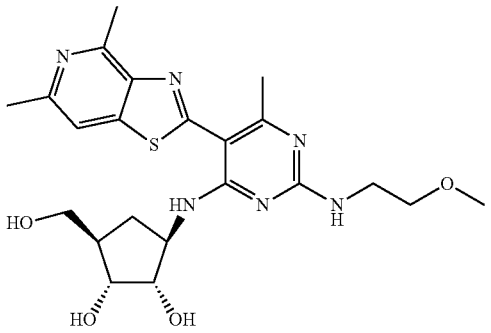
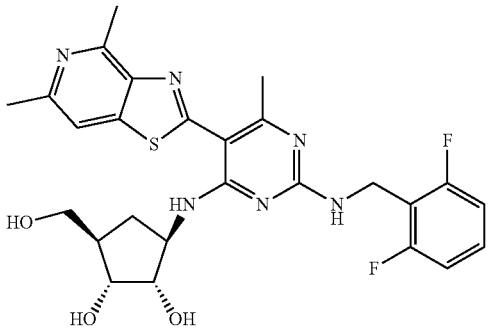
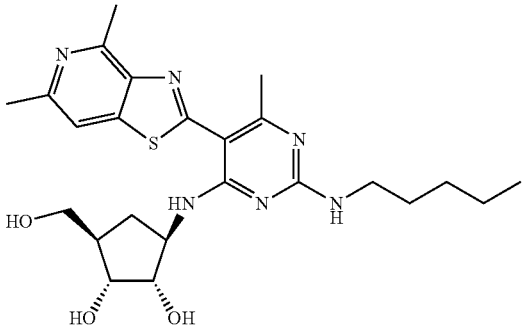
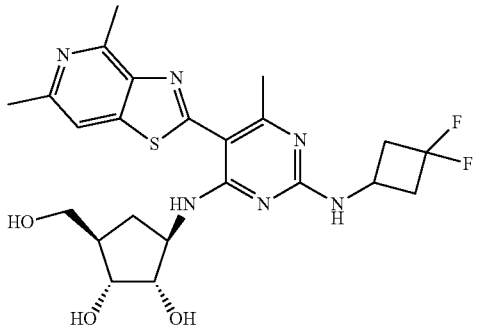
3416	
3417	
3418	
3419	

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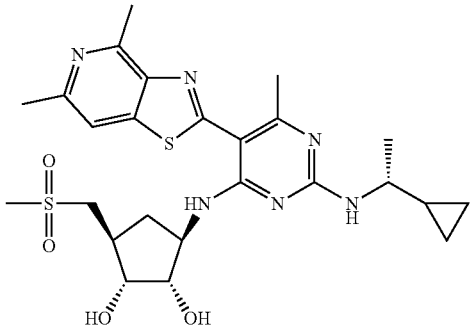
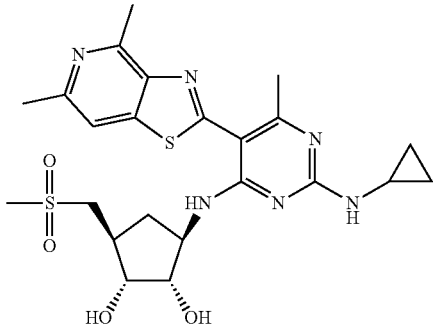
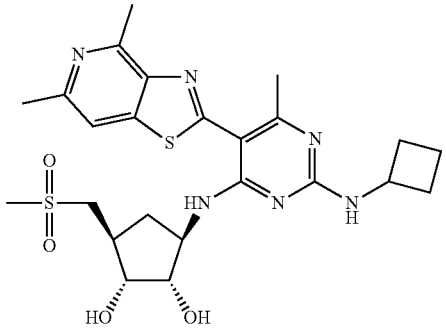
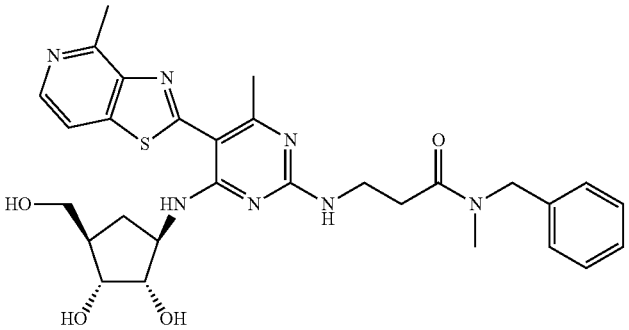
3421	
3425	
3426	
3427	

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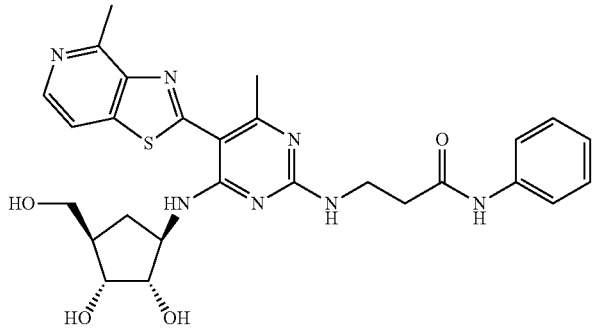
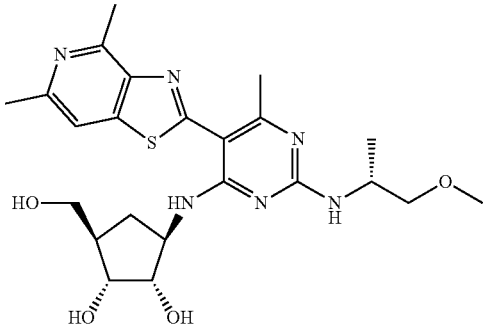
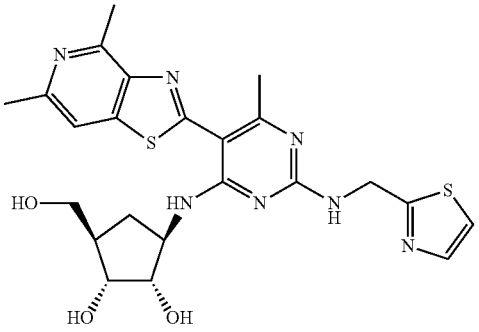
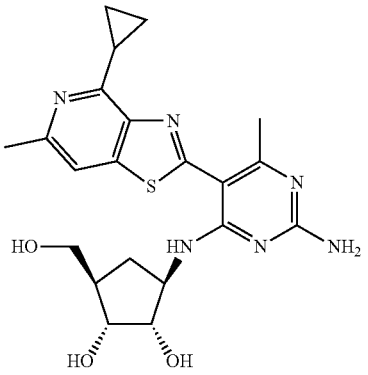
3428	
3430	
3431	
3432	

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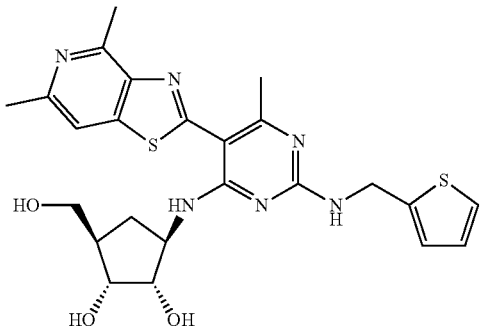
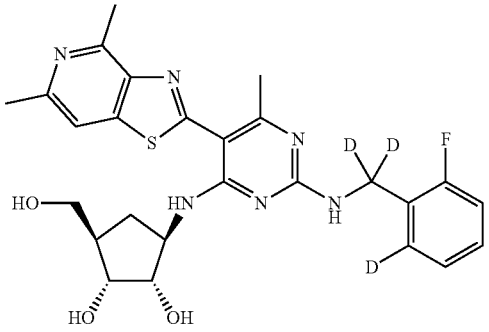
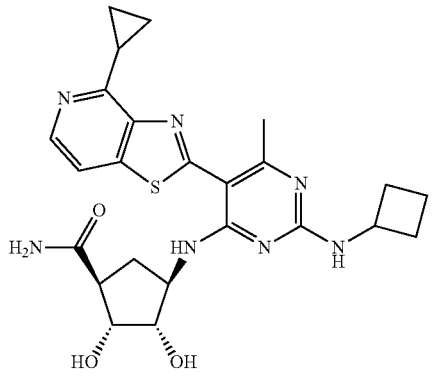
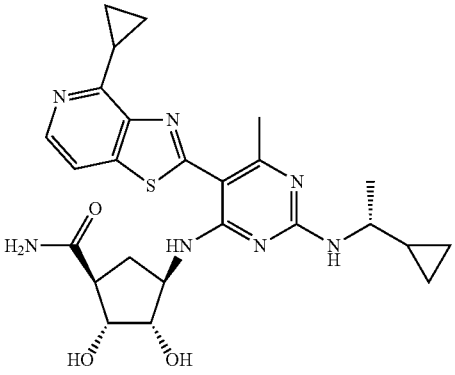
3433	
3434	
3435	
3436	

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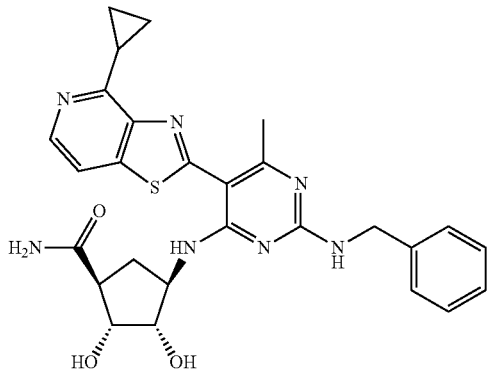
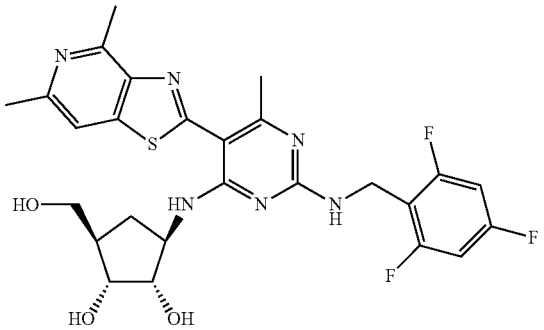
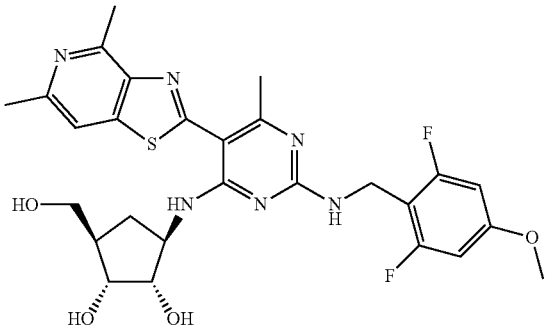
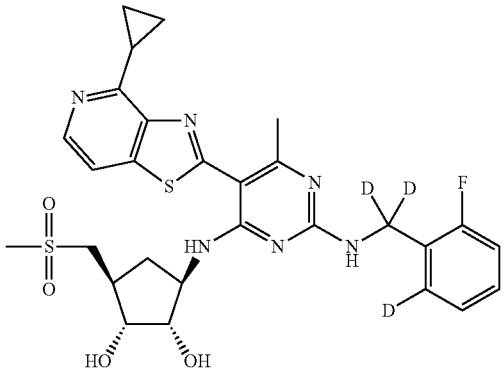
Compd #	Structure
3437	
3438	
3439	
3440	

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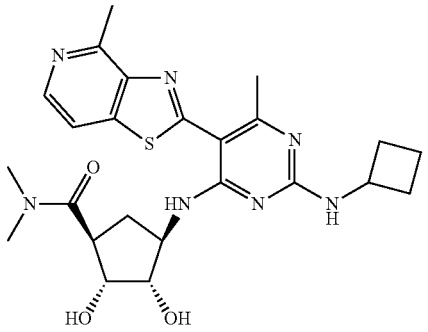
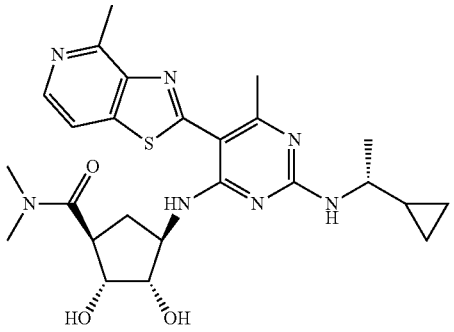
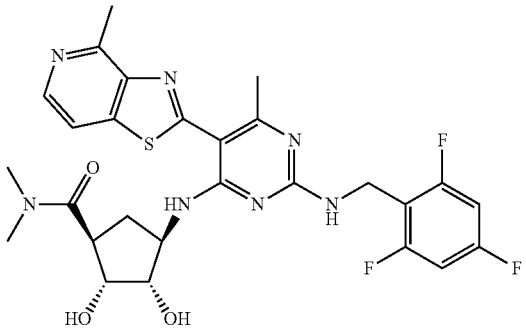
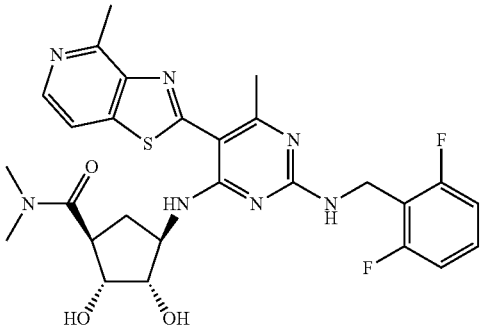
3441	
3442	
3443	
3444	

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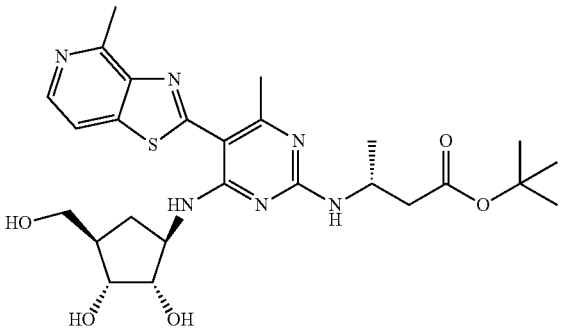
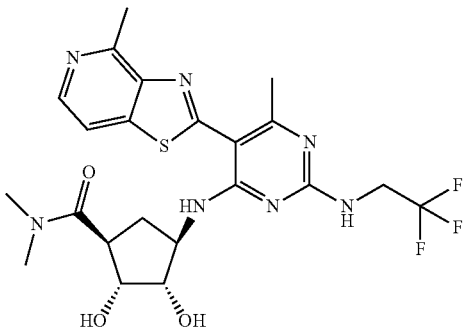
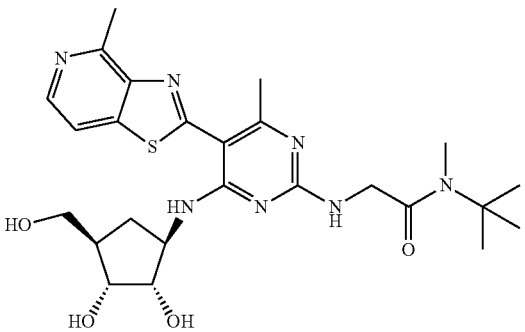
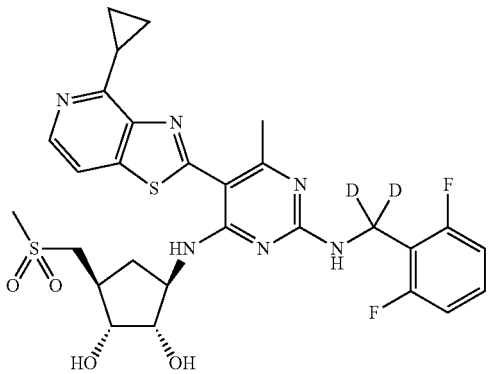
Compd #	Structure
3445	
3446	
3447	
3448	

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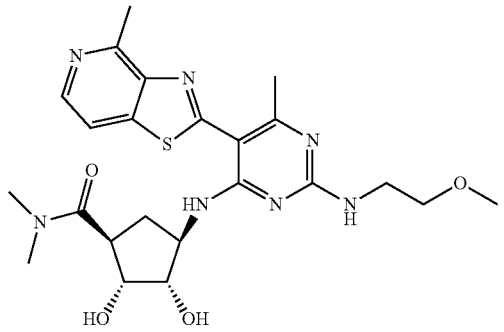
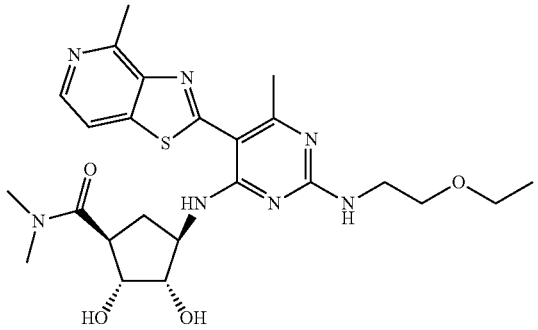
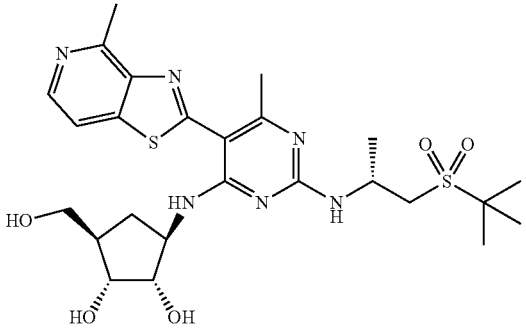
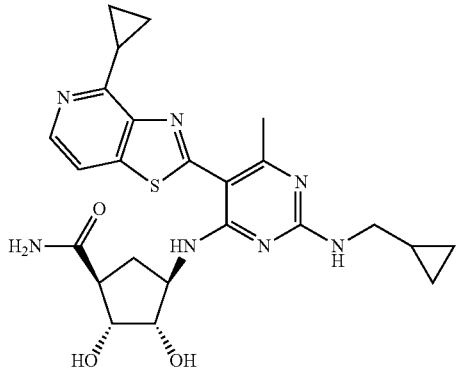
Compd #	Structure
3449	
3450	
3451	
3453	

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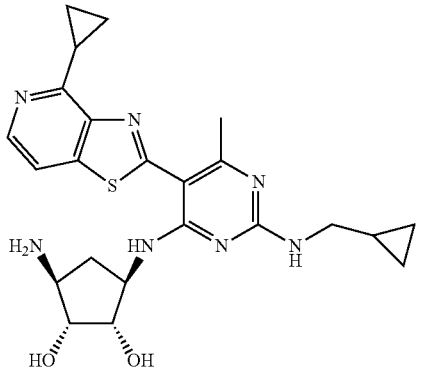
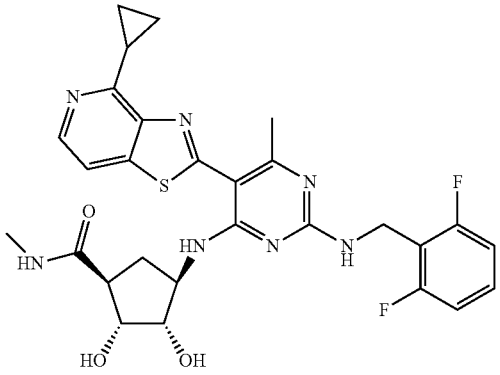
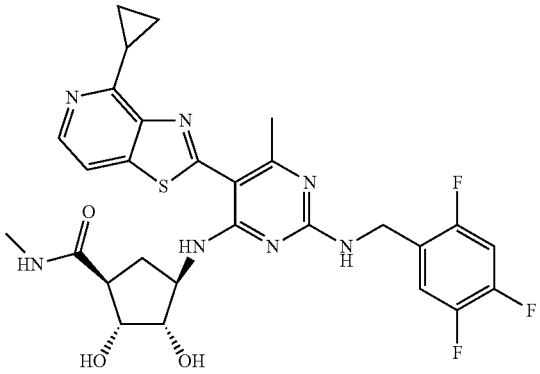
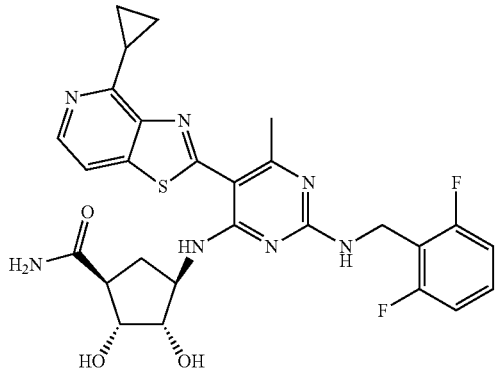
Compd #	Structure
3454	
3455	
3456	
3457	

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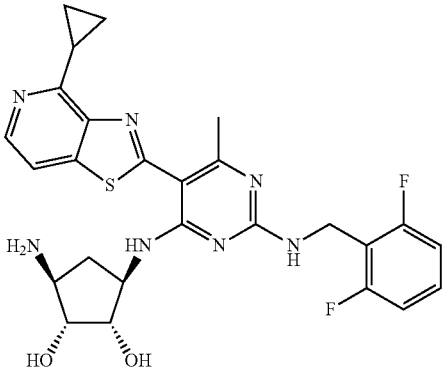
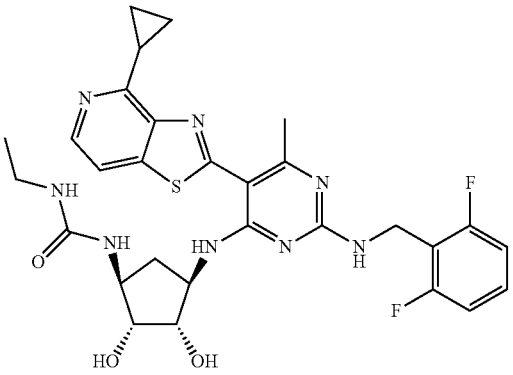
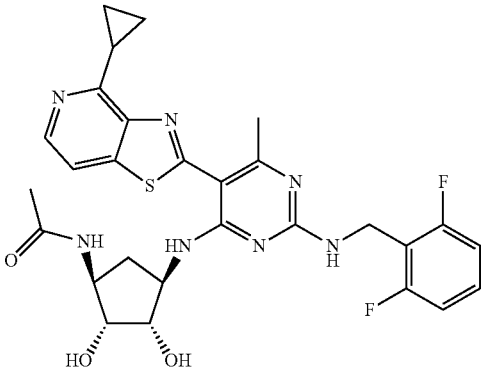
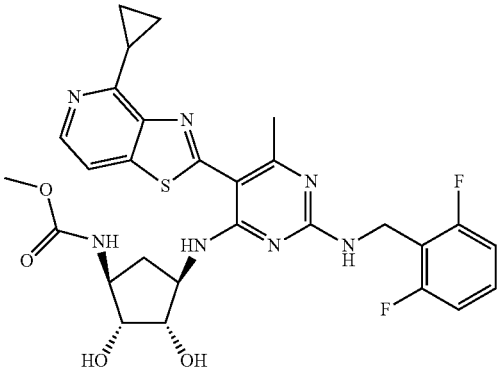
Compd #	Structure
3458	
3459	
3460	
3461	

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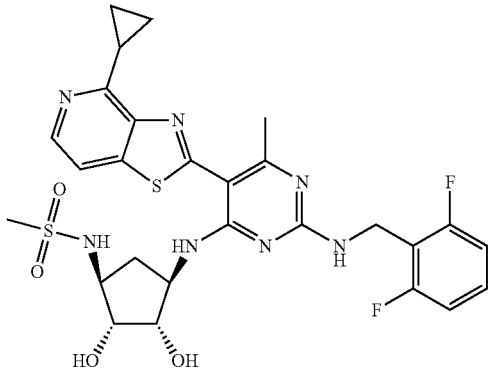
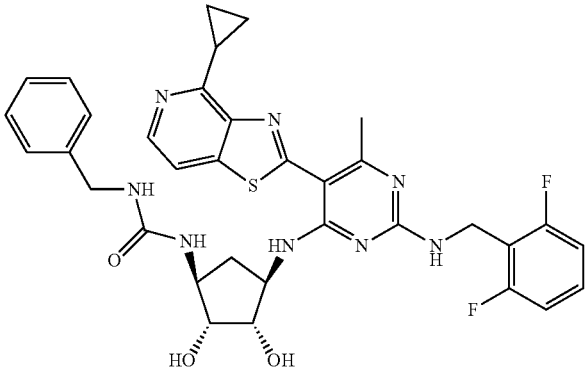
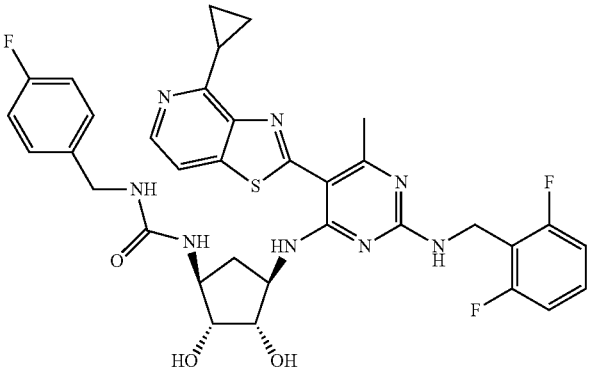
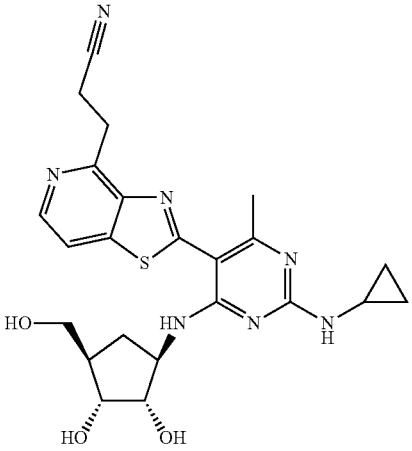
Compd #	Structure
3462	
3463	
3464	
3501	

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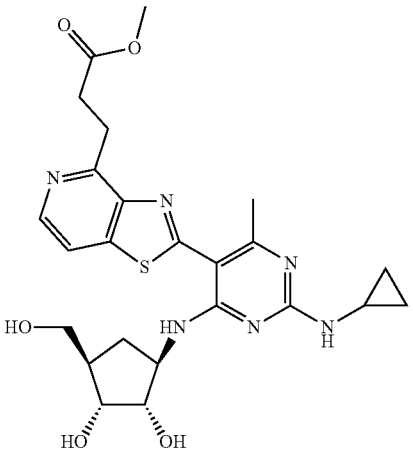
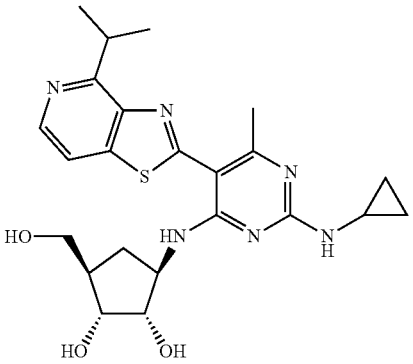
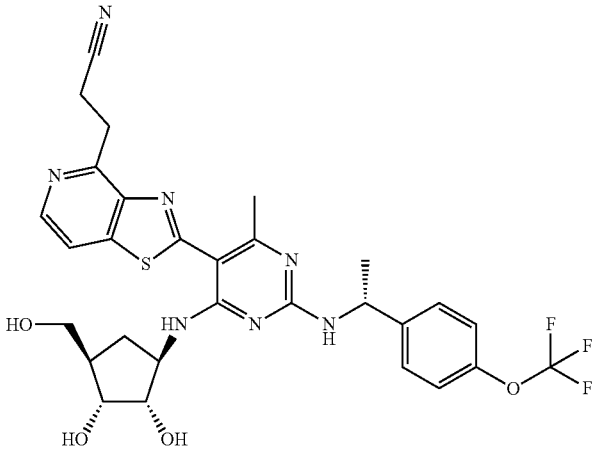
Compd #	Structure
3502	
3503	
3504	

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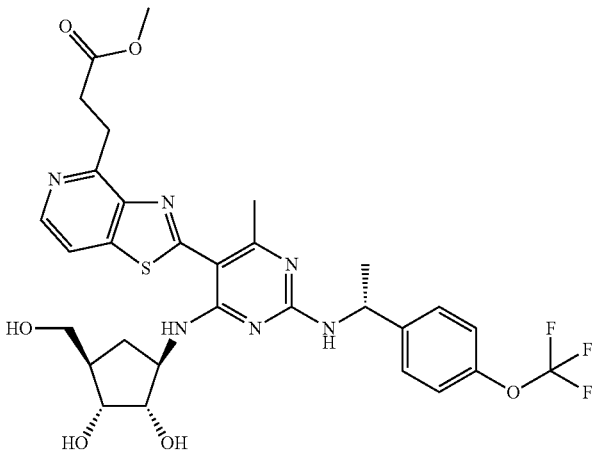
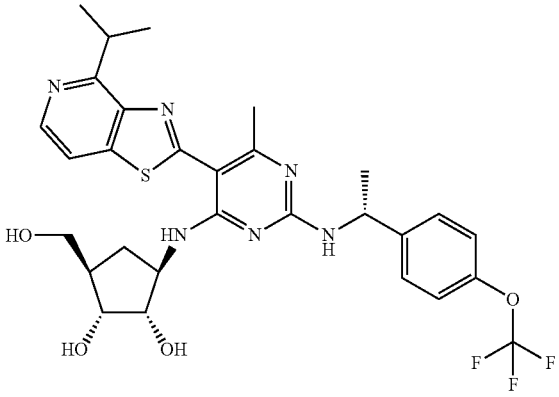
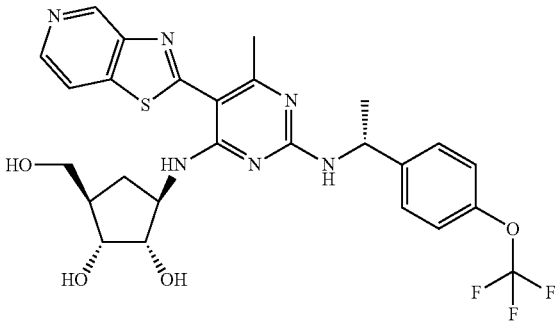
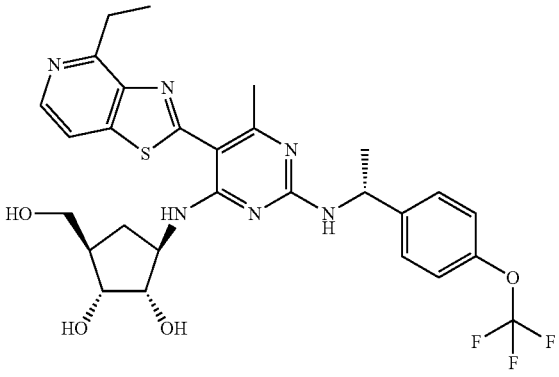
3505	
3506	
3507	
3508	

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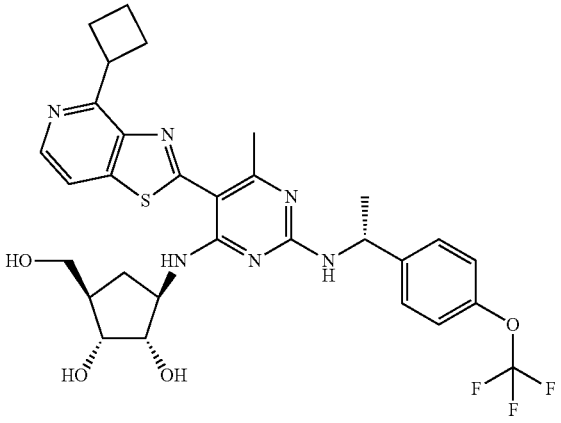
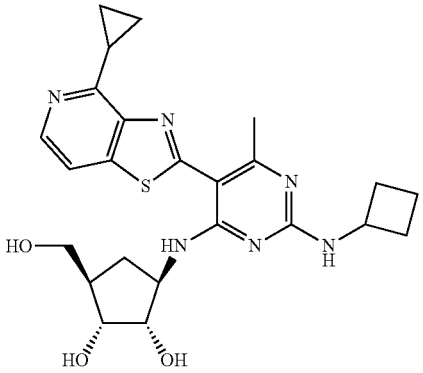
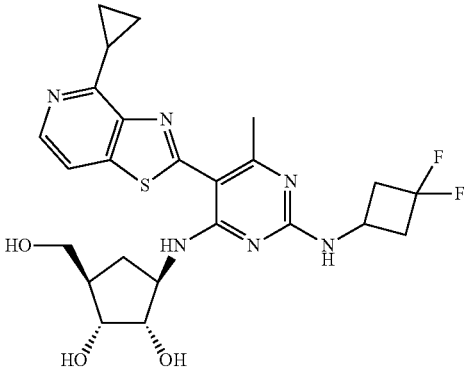
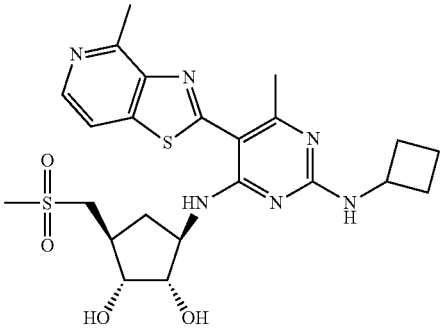
Compd #	Structure
3509	
3510	
3511	
3512	

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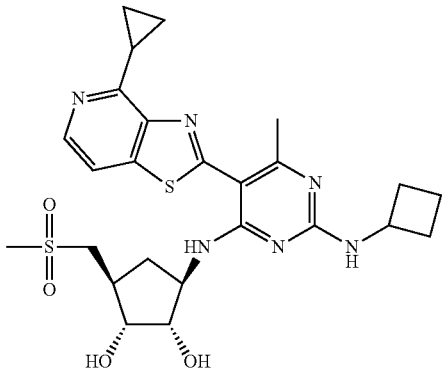
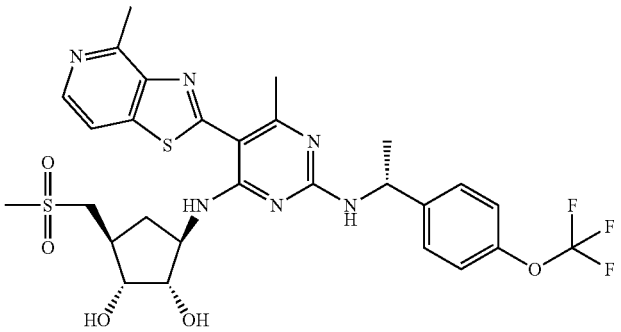
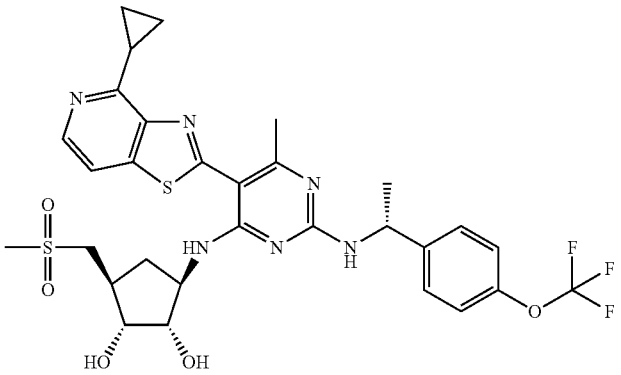
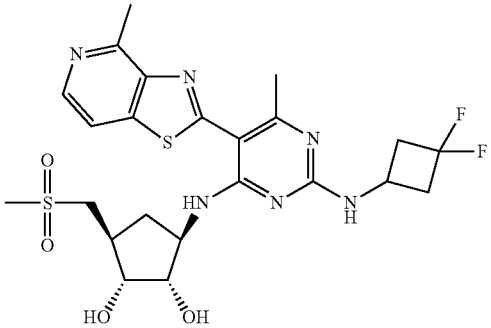
Compd #	Structure
3513	
3514	
3515	
3516	

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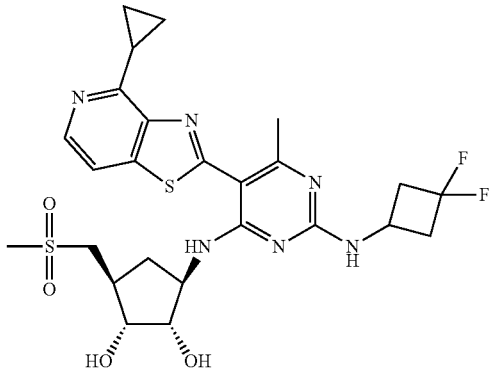
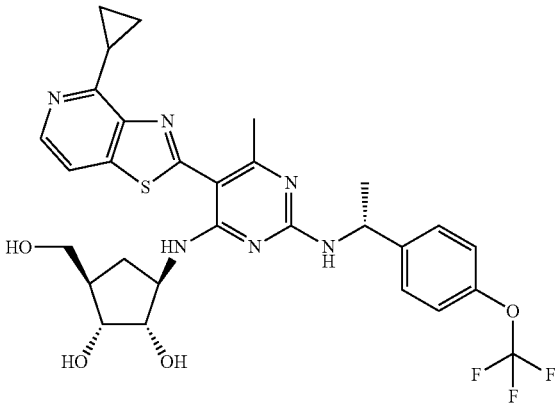
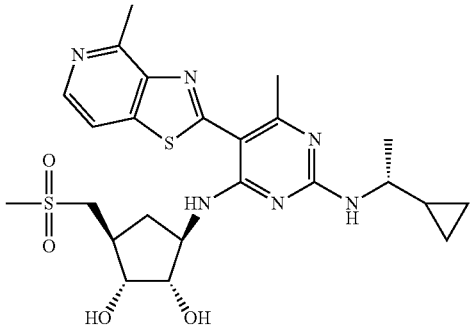
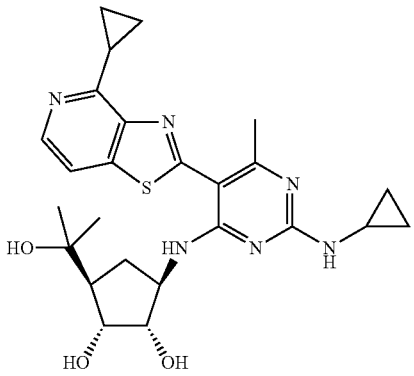
3517	
3518	
3519	
3520	

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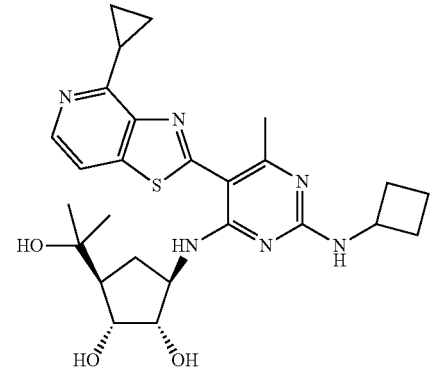
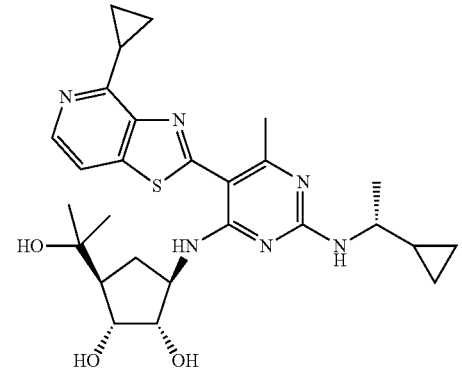
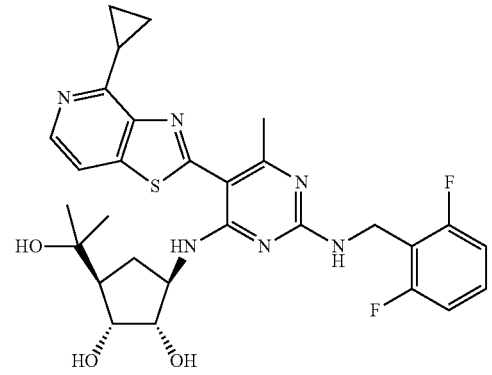
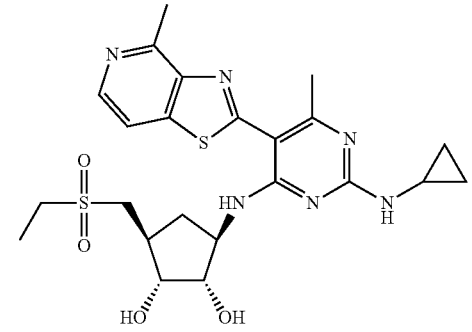
3521	
3522	
3523	
3524	

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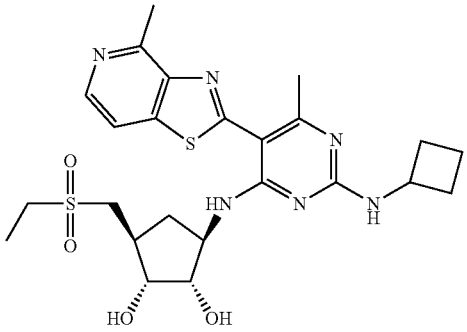
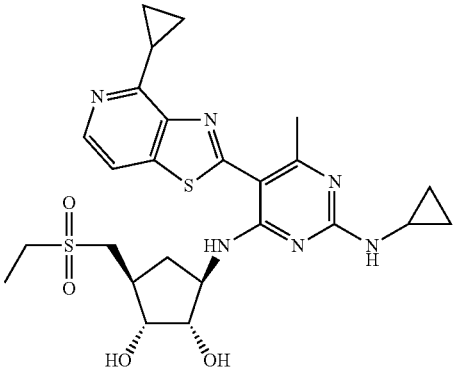
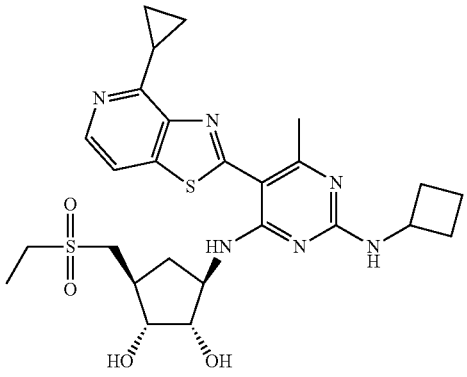
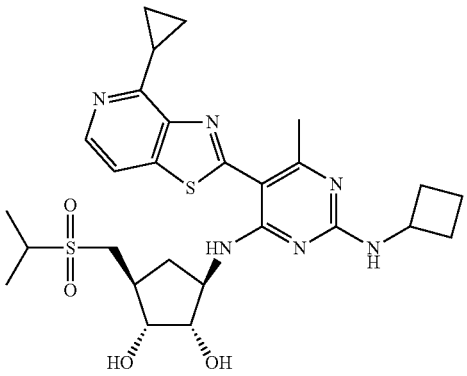
Compd #	Structure
3525	
3526	
3527	
3528	

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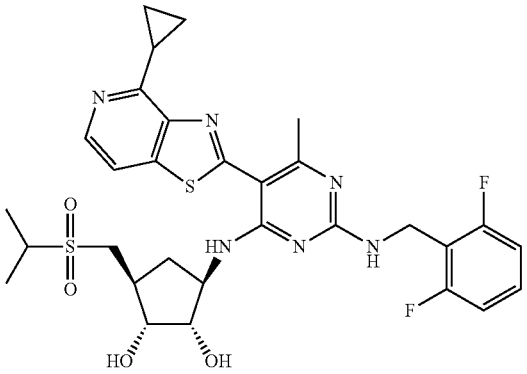
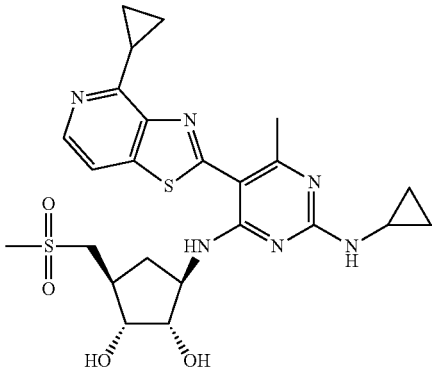
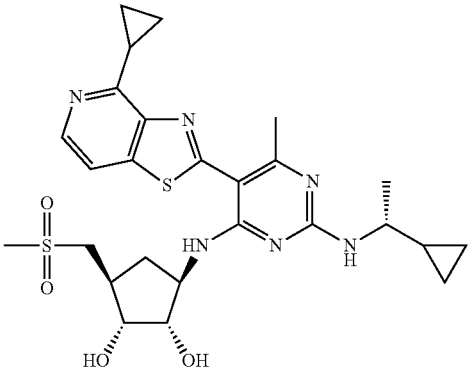
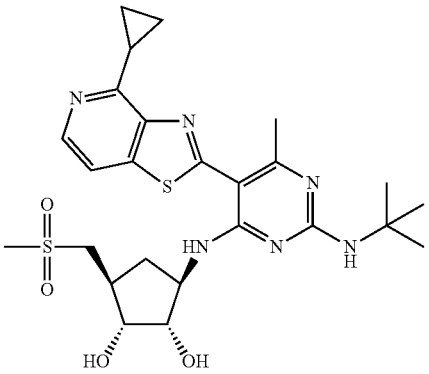
3529	
3530	
3531	
3532	

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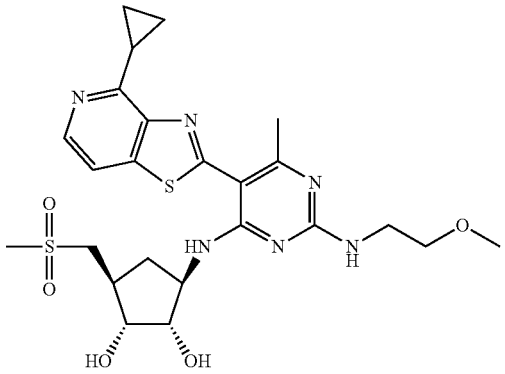
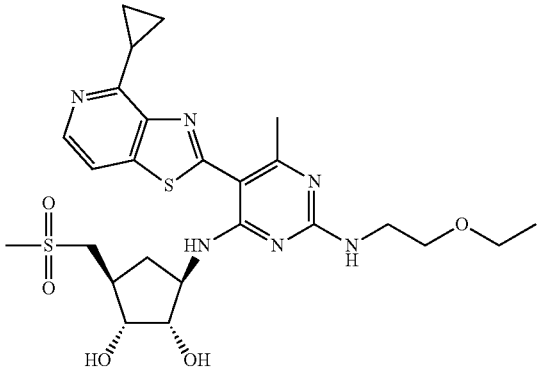
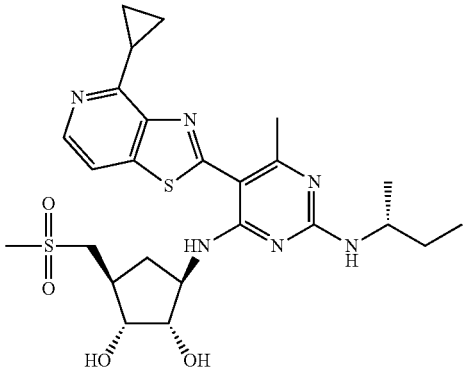
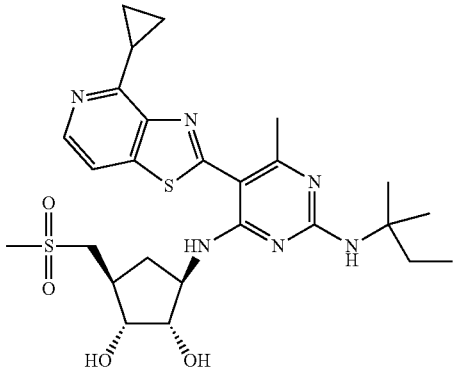
3533	
3534	
3535	
3536	

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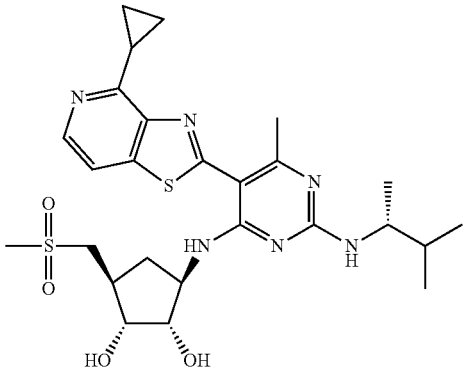
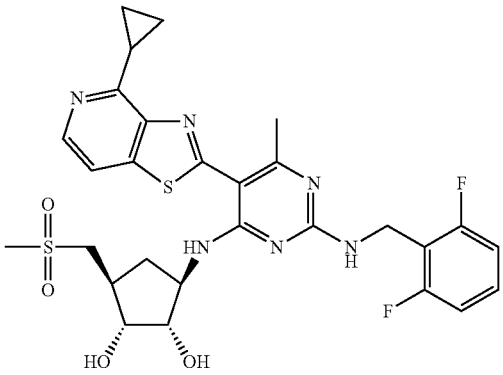
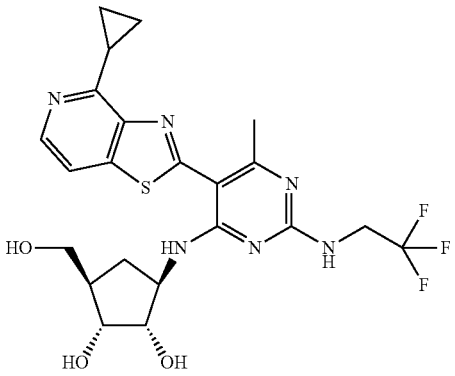
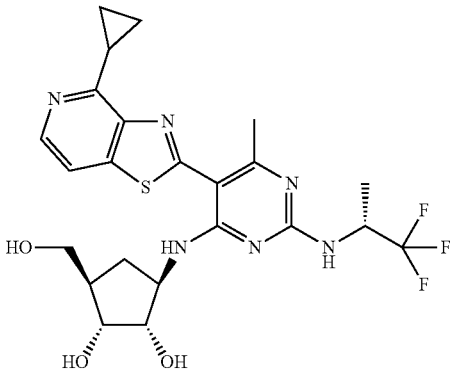
3537	
3538	
3539	
3540	

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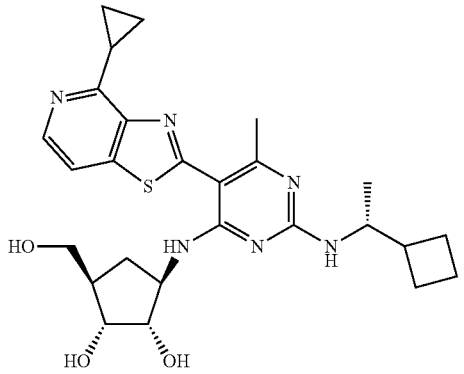
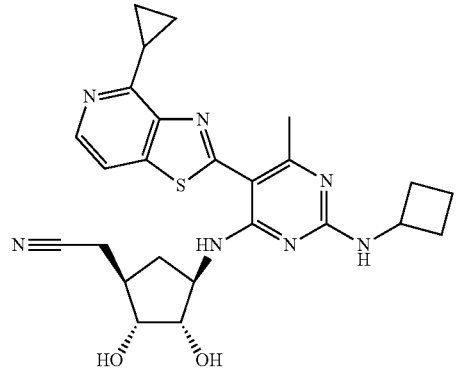
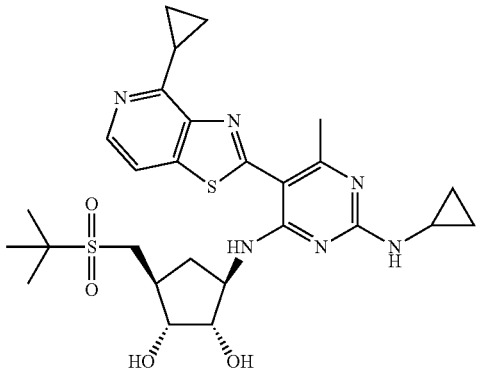
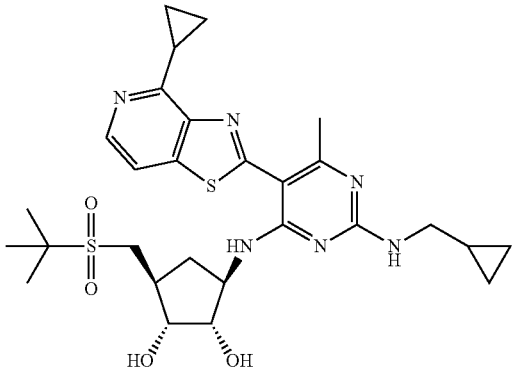
3541	
3542	
3543	
3544	

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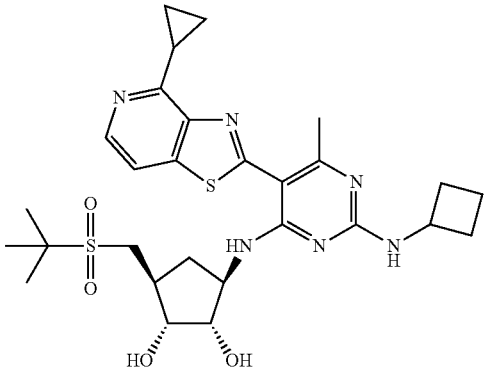
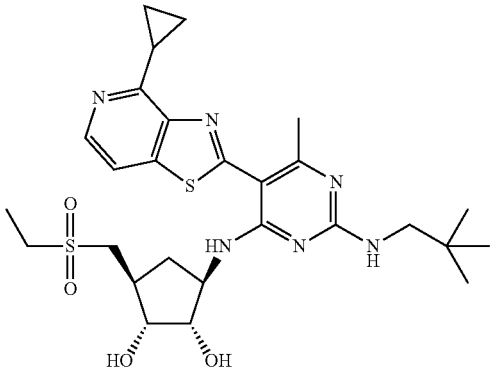
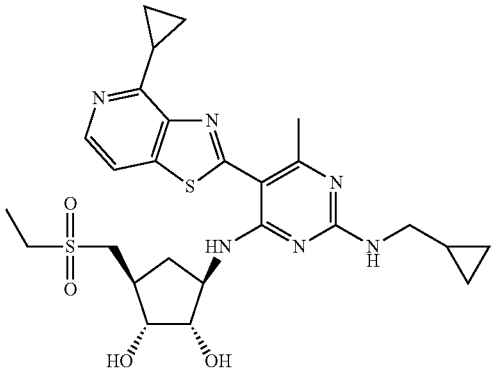
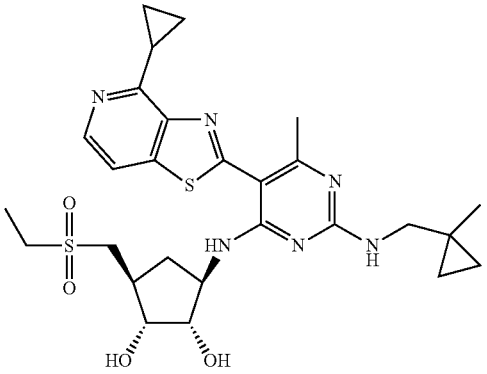
3545	
3546	
3547	
3548	

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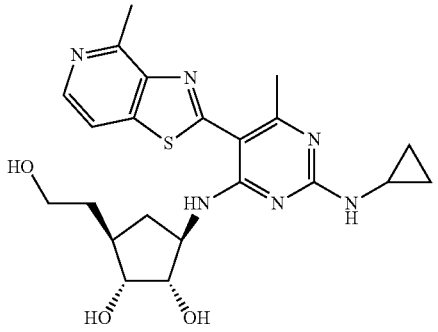
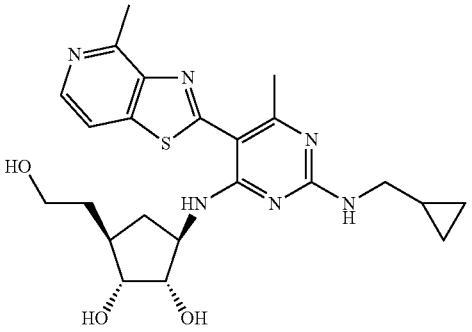
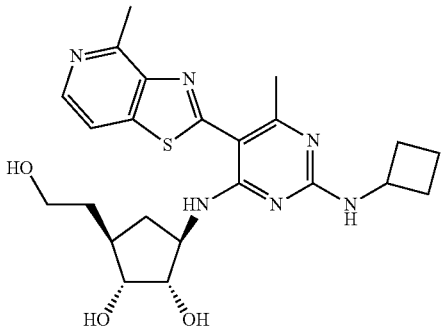
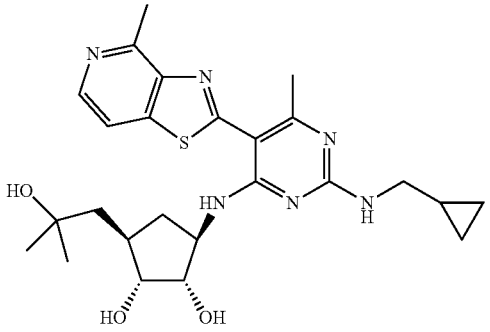
3549	
3550	
3551	
3552	

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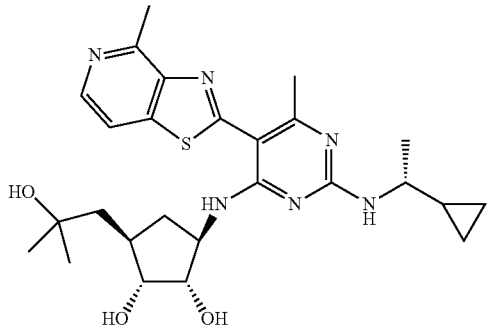
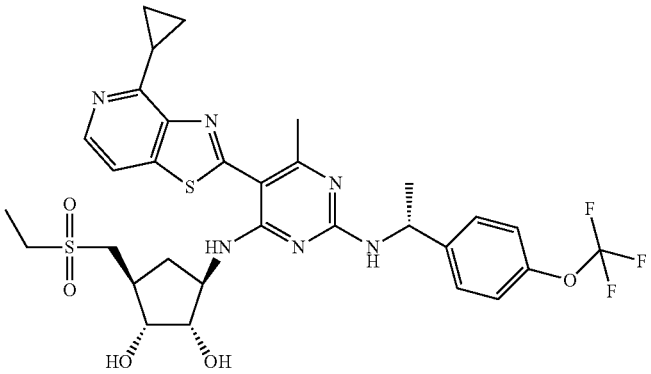
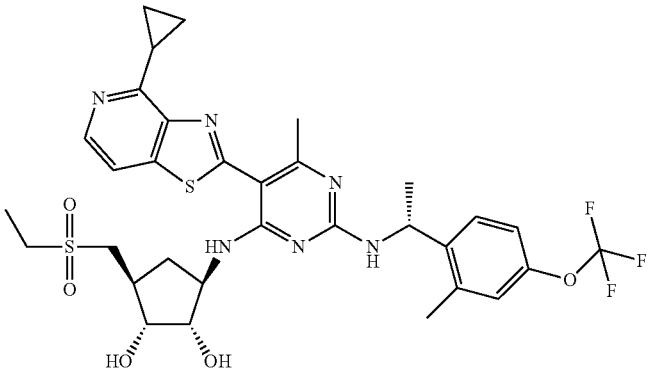
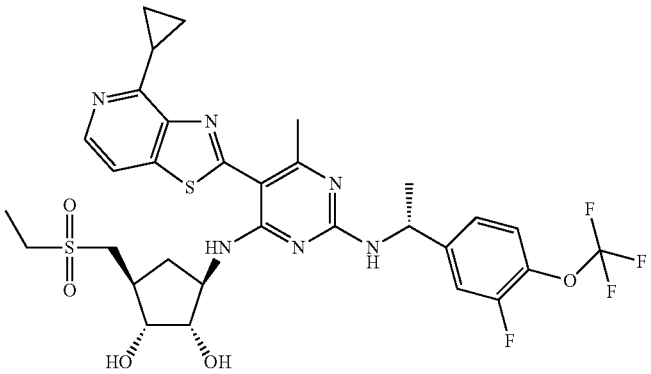
3553	
3554	
3555	
3556	

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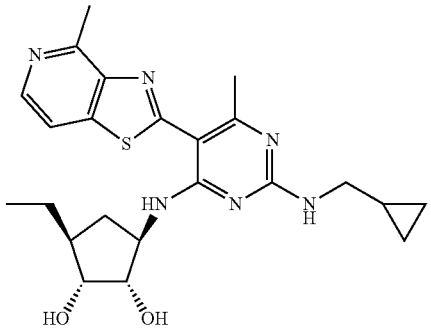
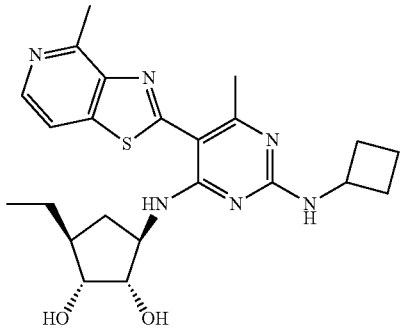
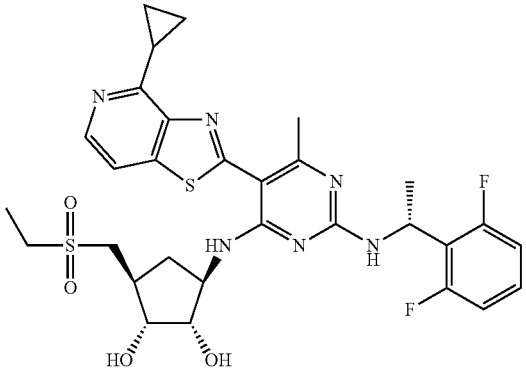
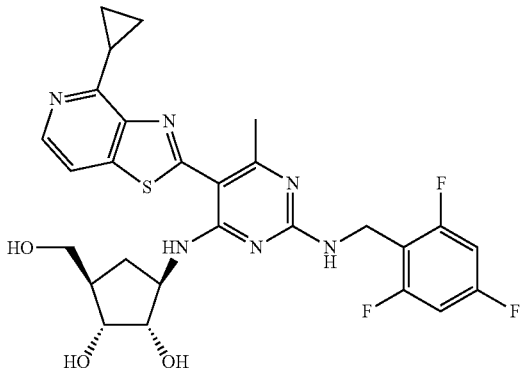
3557	
3558	
3560	
3565	

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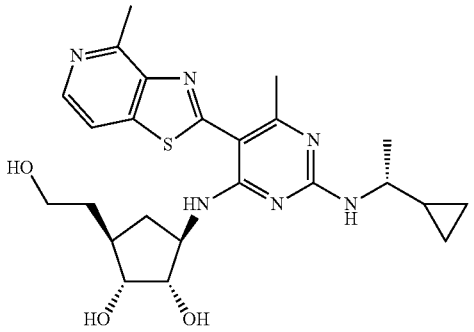
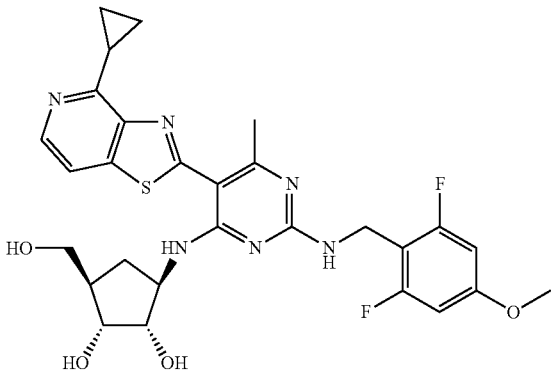
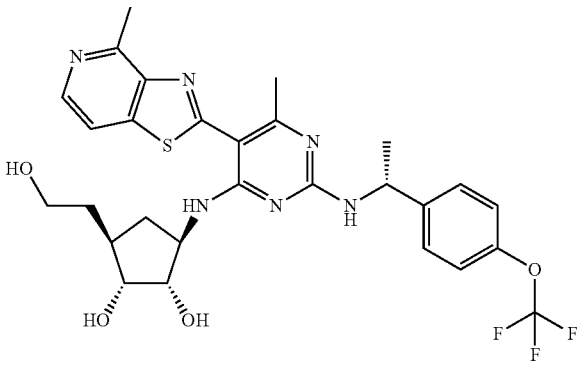
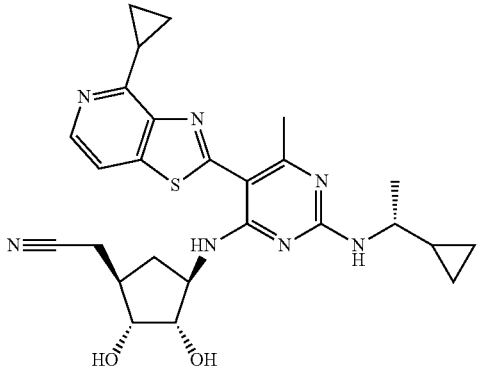
3561	
3566	
3562	
3567	

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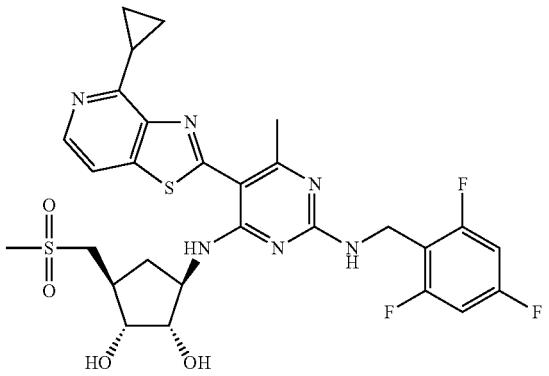
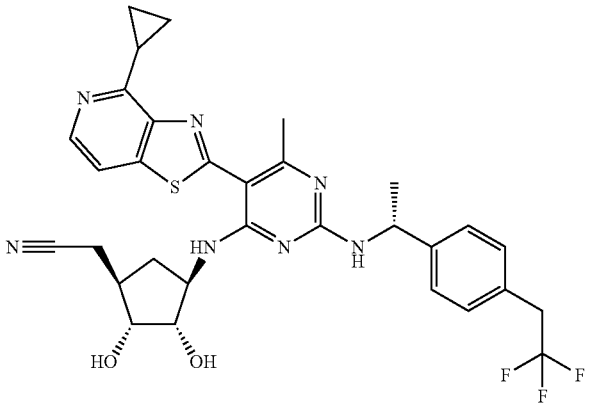
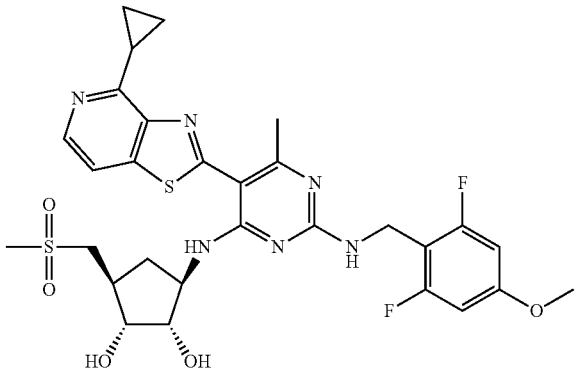
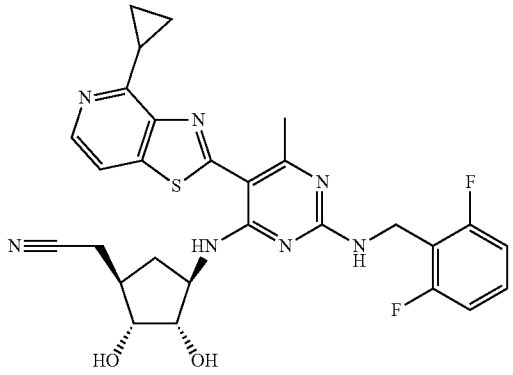
3563	
3568	
3564	
3569	

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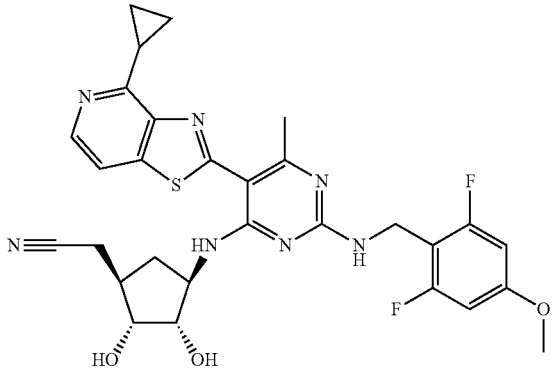
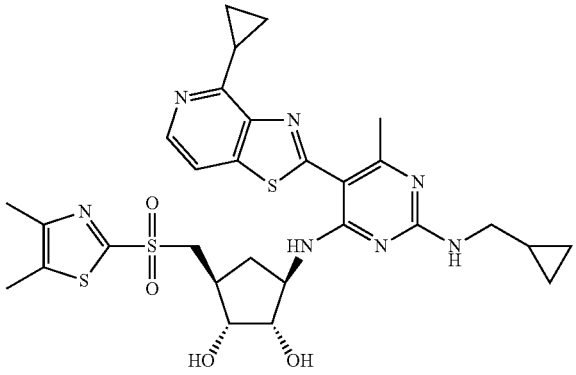
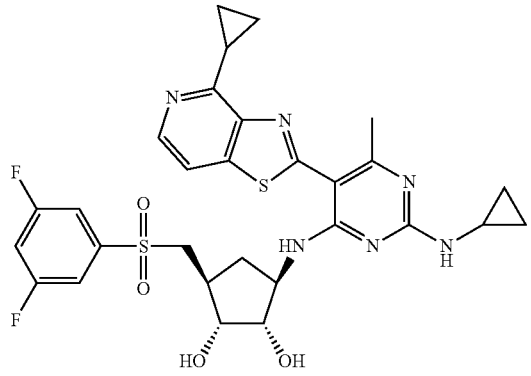
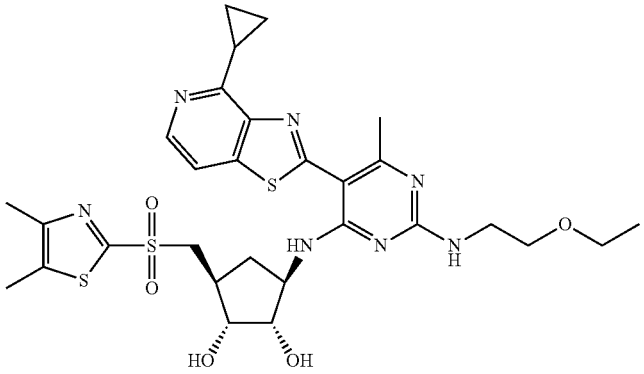
3570	
3576	
3571	
3577	

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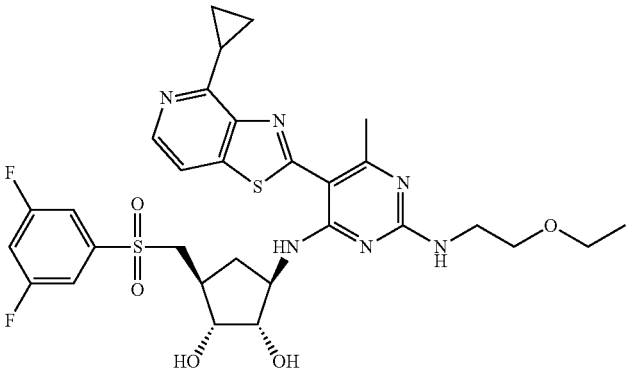
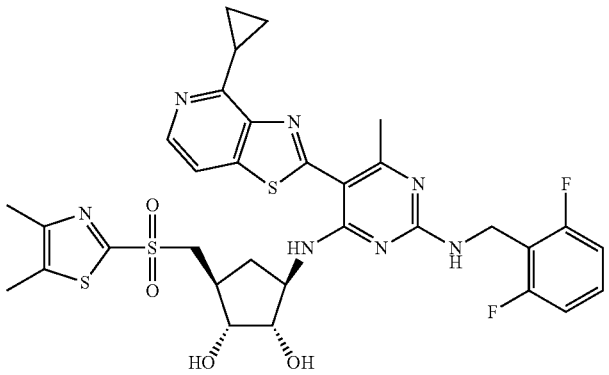
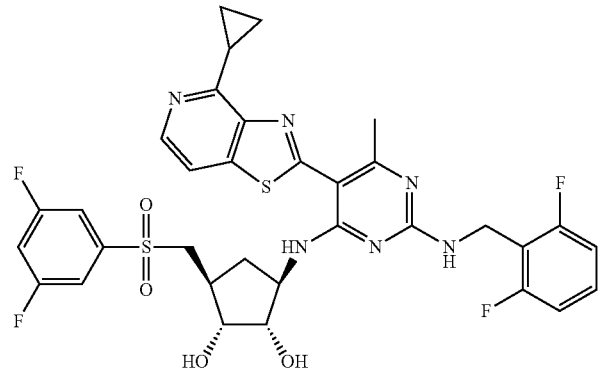
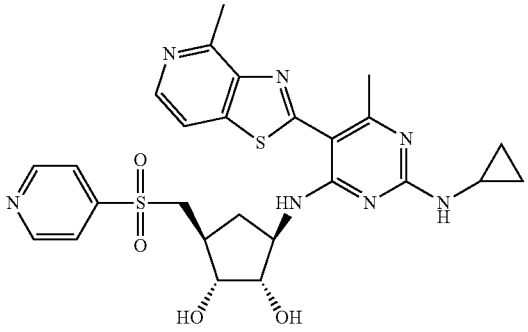
3573	
3578	
3574	
3579	

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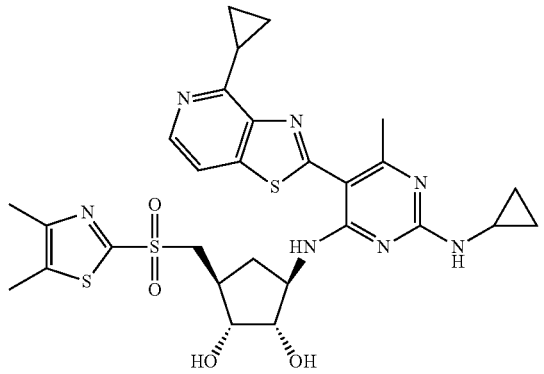
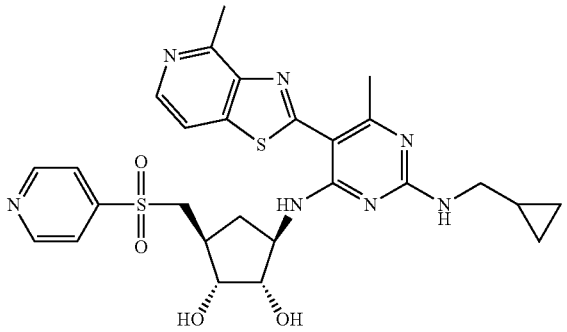
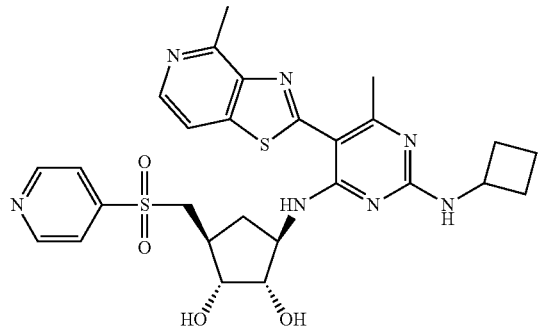
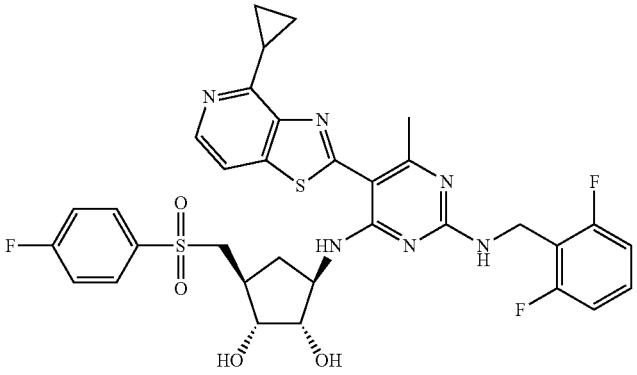
3575	
3580	
3581	
3586	

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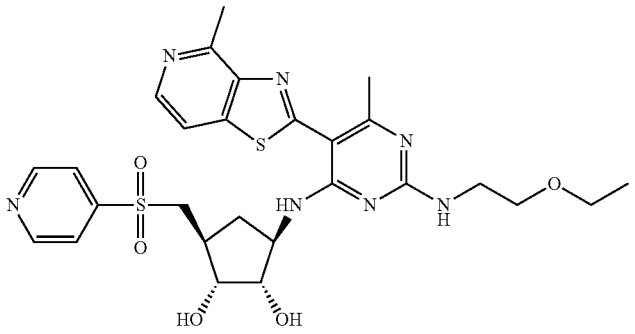
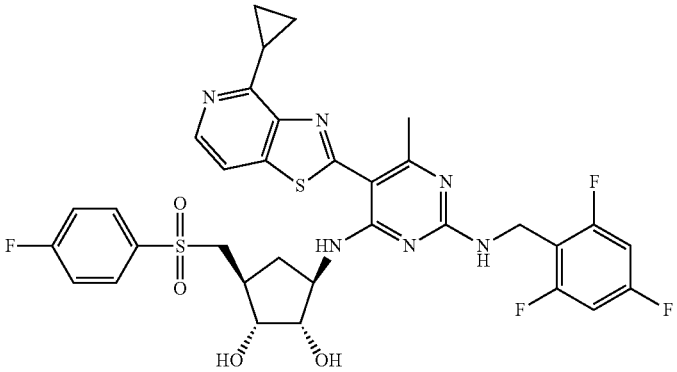
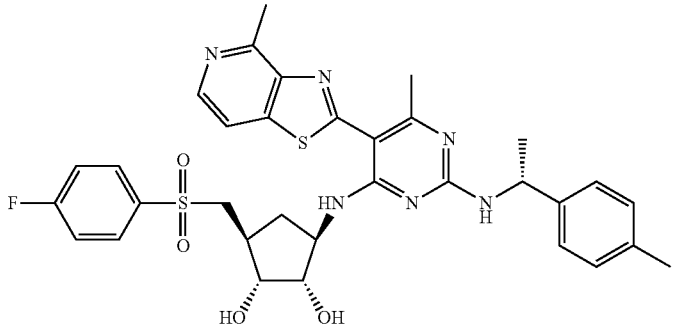
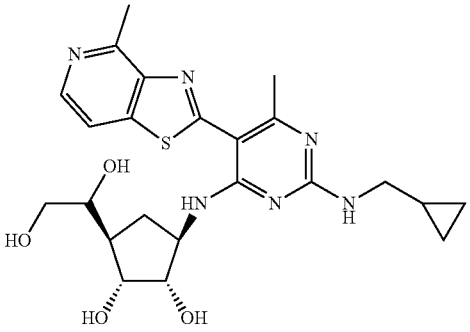
3582	
3587	
3583	
3591	

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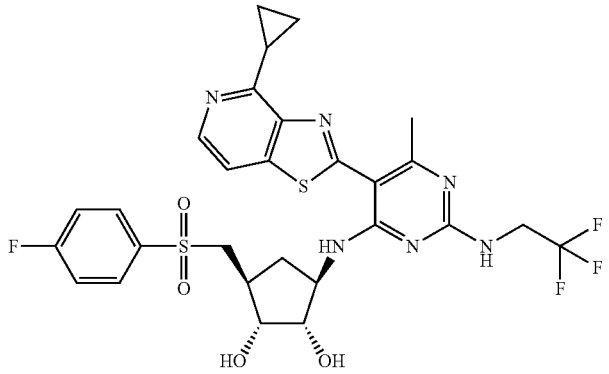
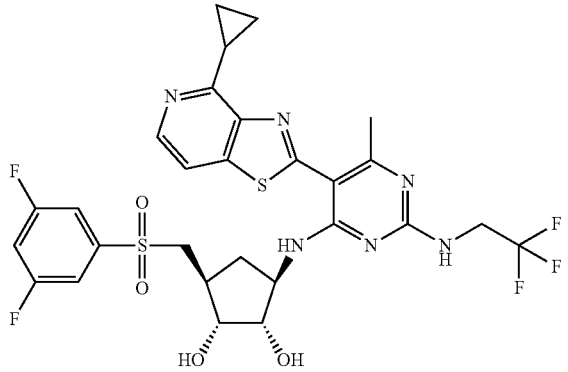
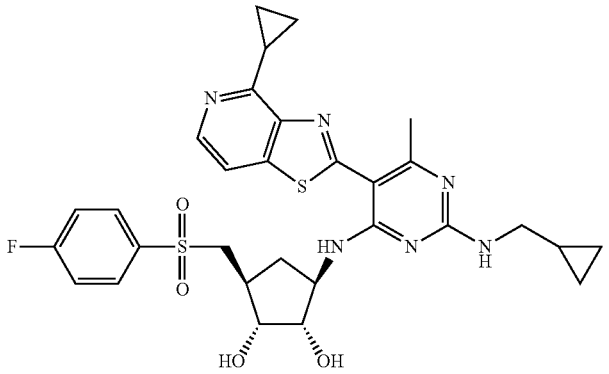
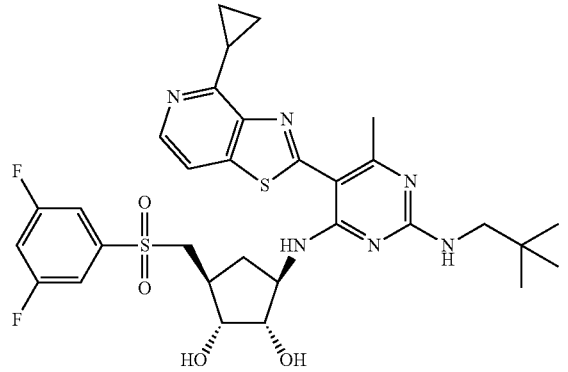
3584	
3592	
3585	
3593	

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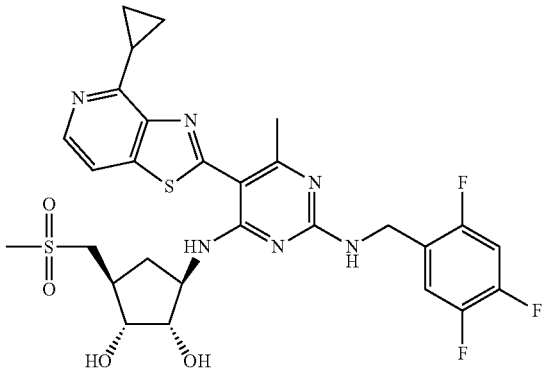
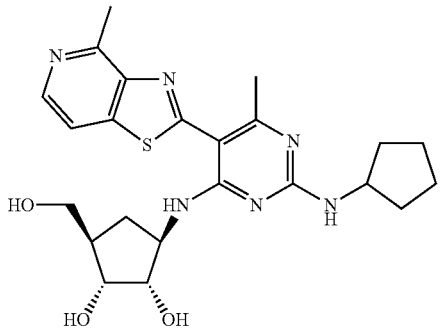
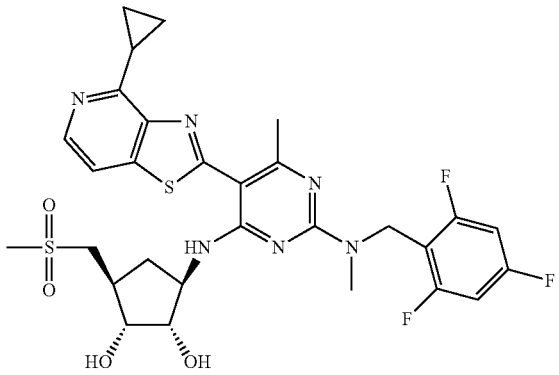
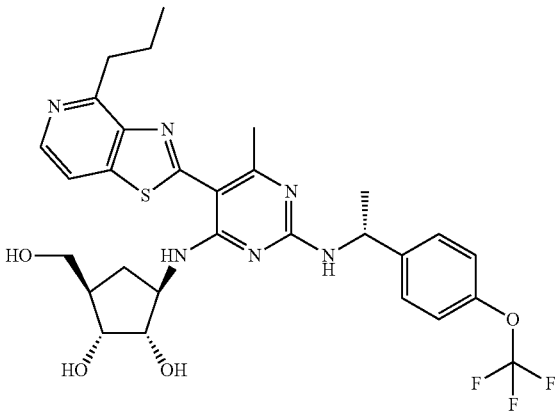
3594	
3704	
3600	
3705	

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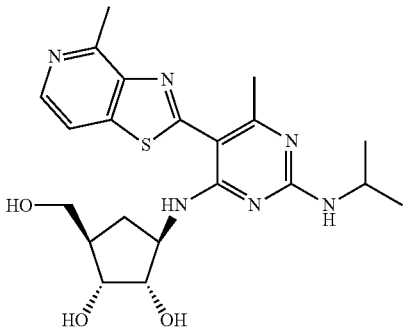
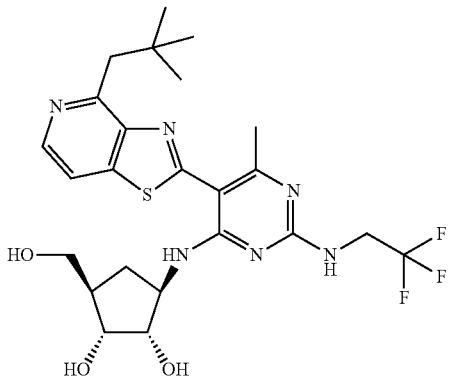
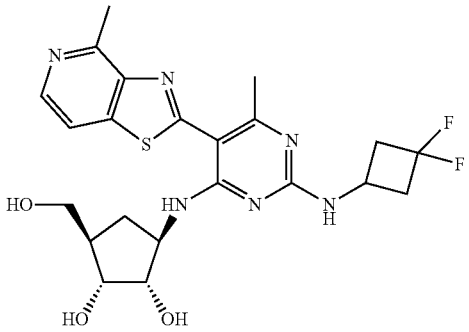
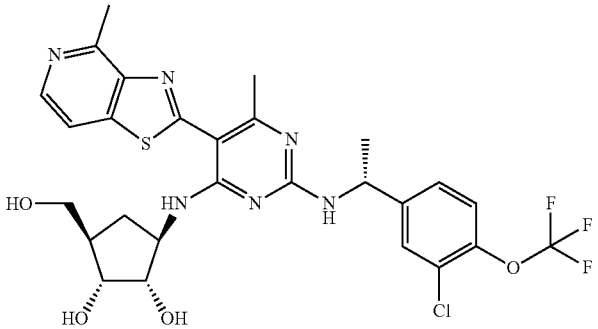
3701	
3706	
3702	
3707	

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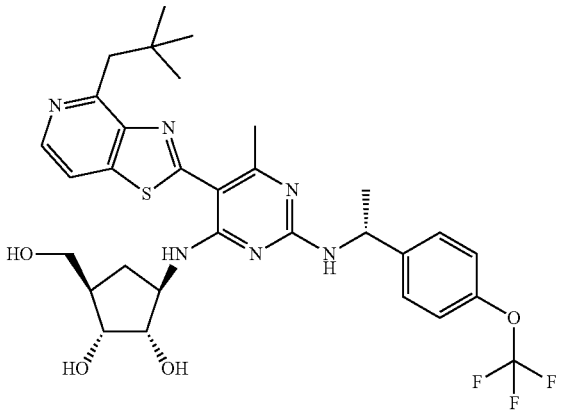
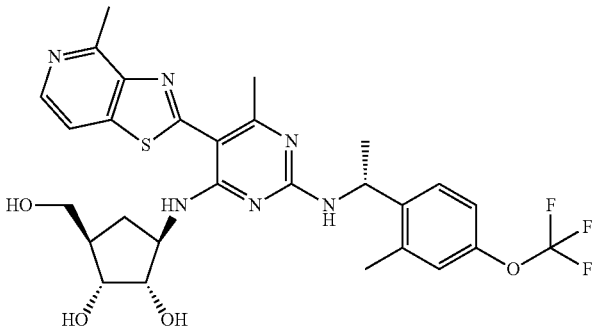
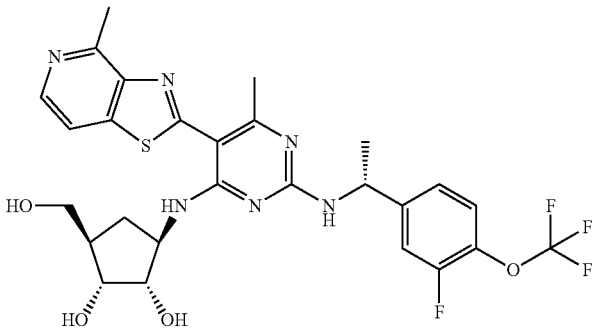
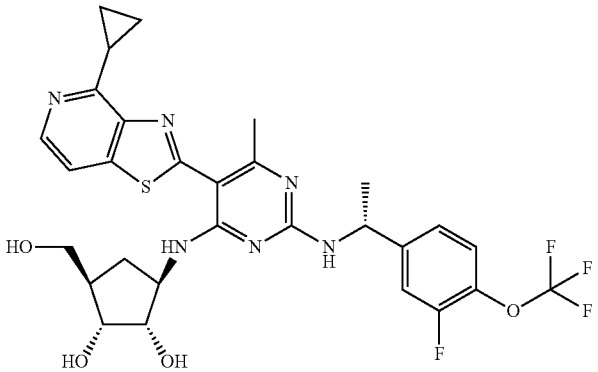
3703	
3708	
3709	
3717	

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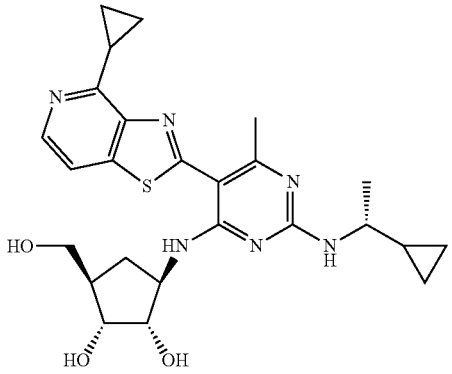
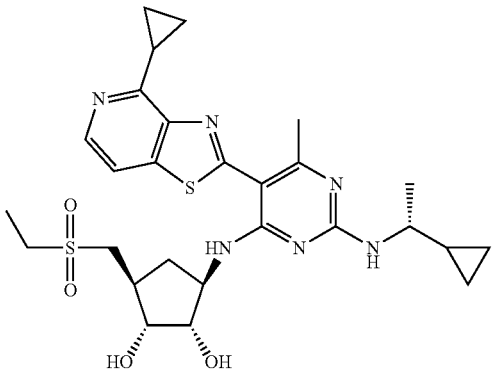
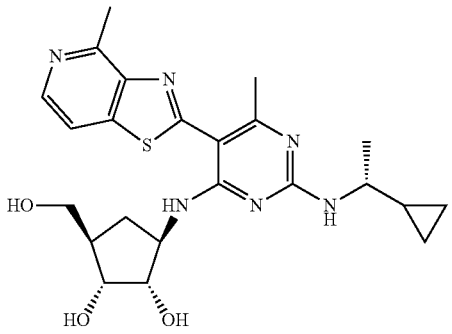
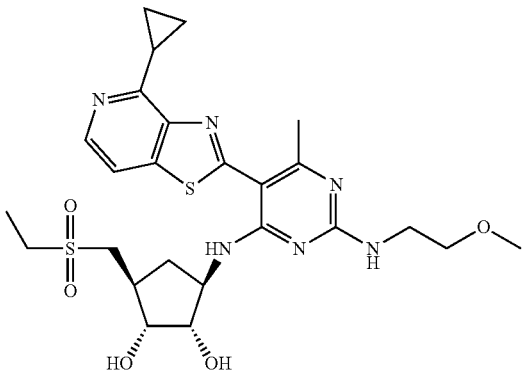
3711	
3718	
3712	
3719	

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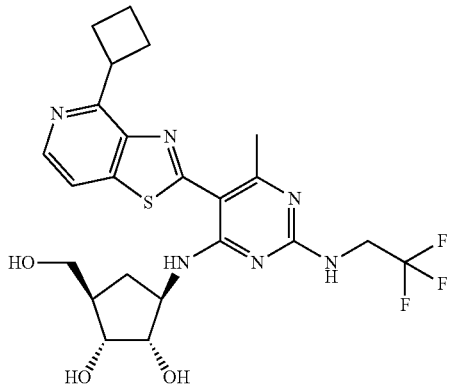
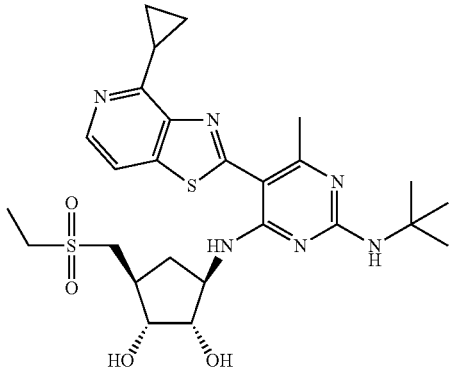
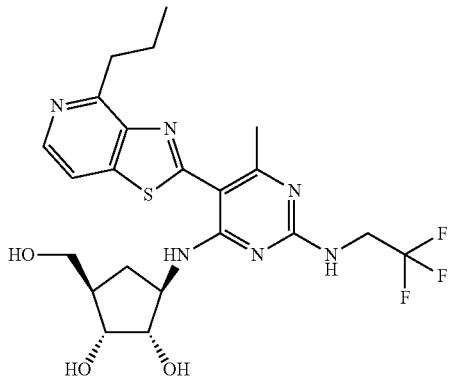
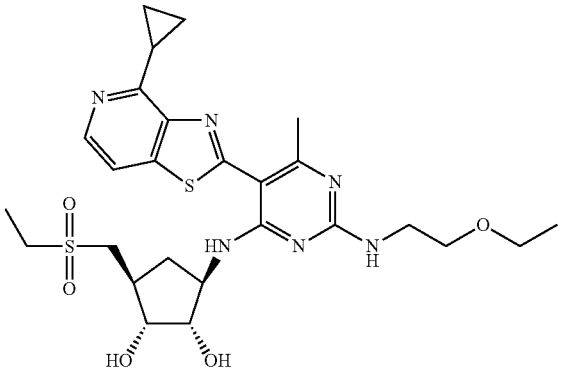
3714	
3720	
3715	
3721	

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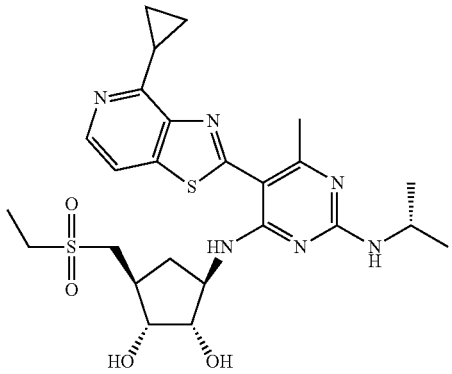
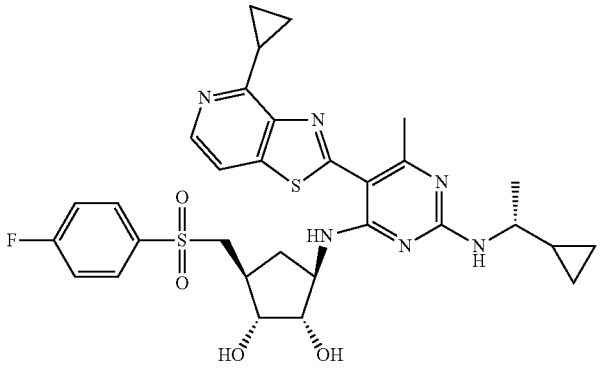
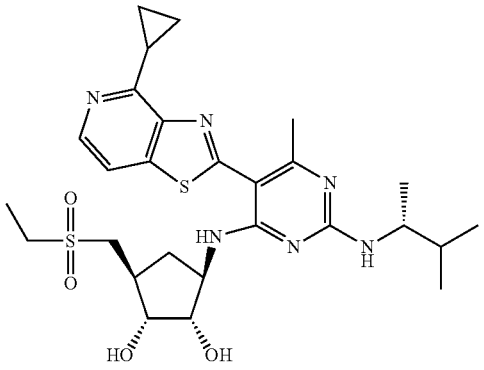
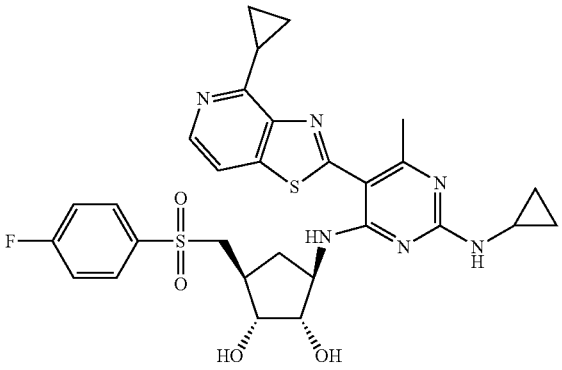
3722	
3727	
3723	
3728	

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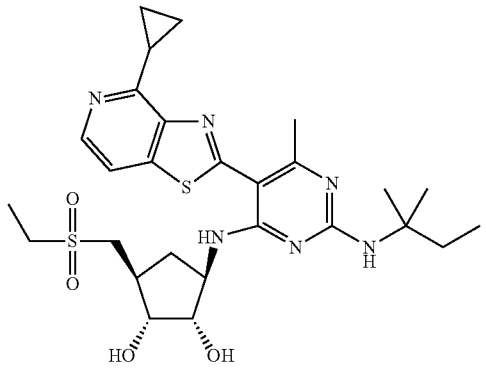
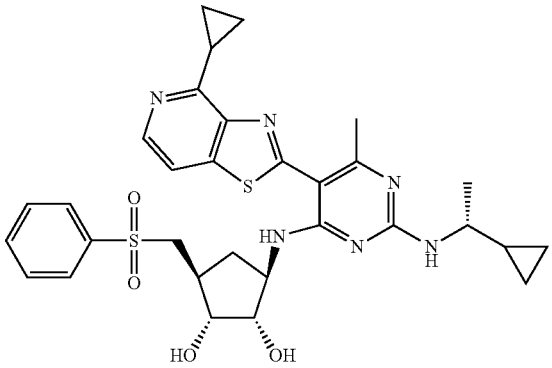
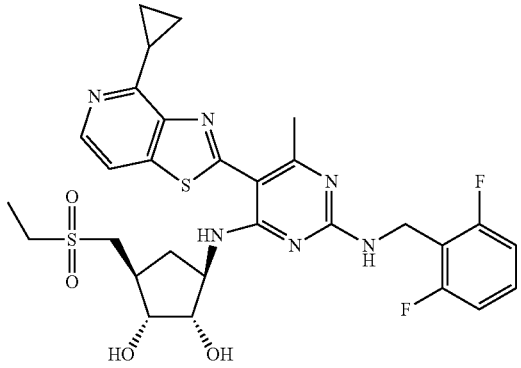
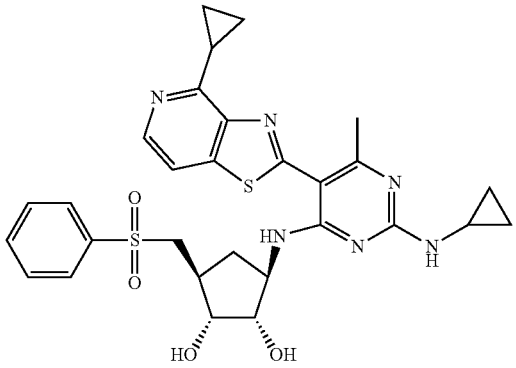
3724	
3729	
3725	
3730	

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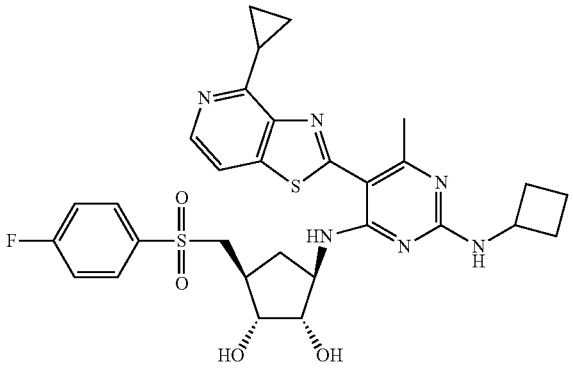
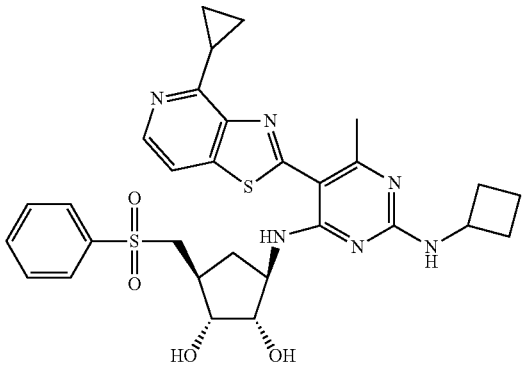
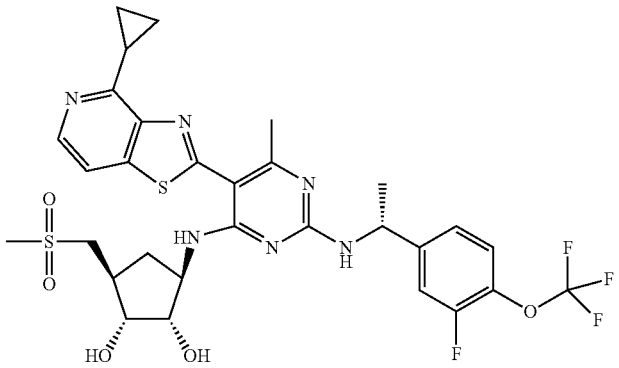
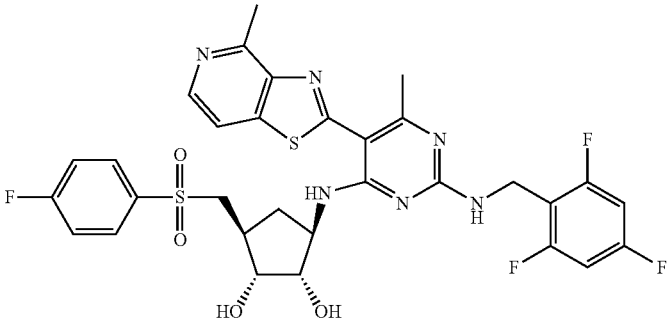
3726	
3731	
3732	
3737	

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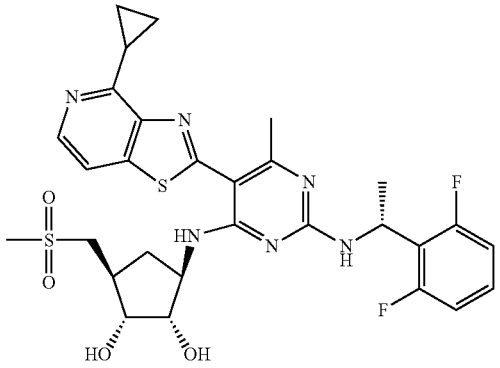
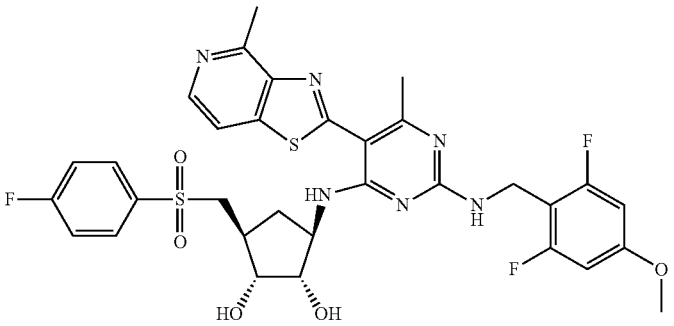
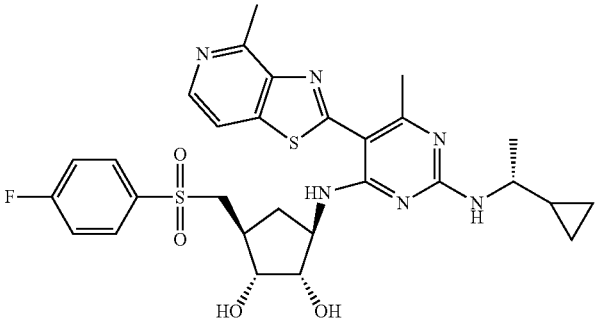
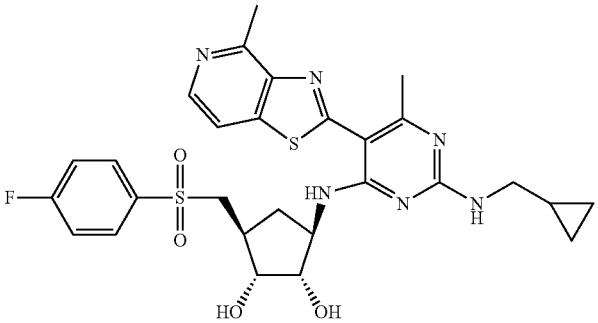
3733	
3738	
3734	
3739	

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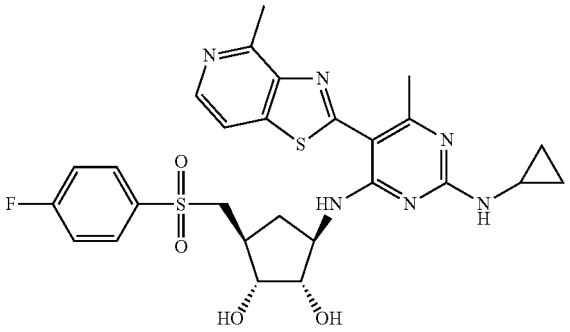
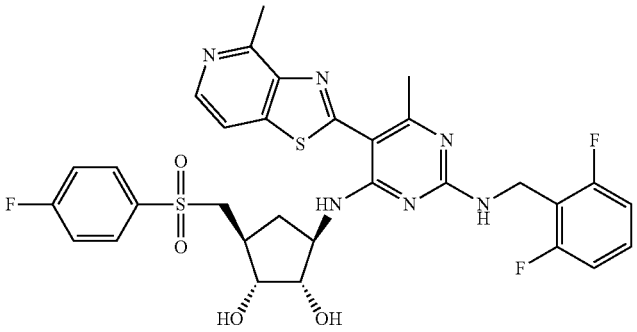
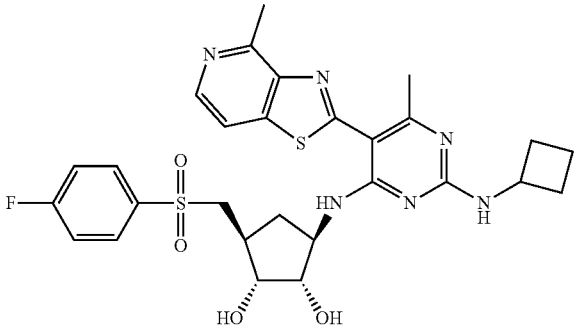
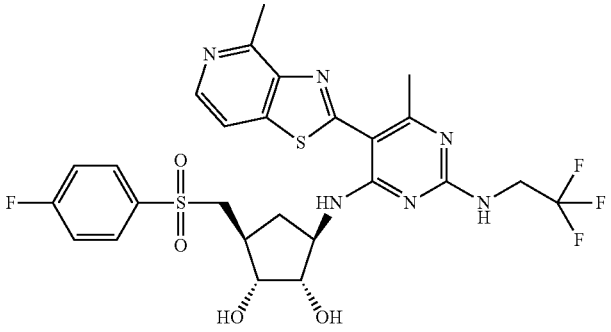
Compd #	Structure
3735	
3740	
3736	
3741	

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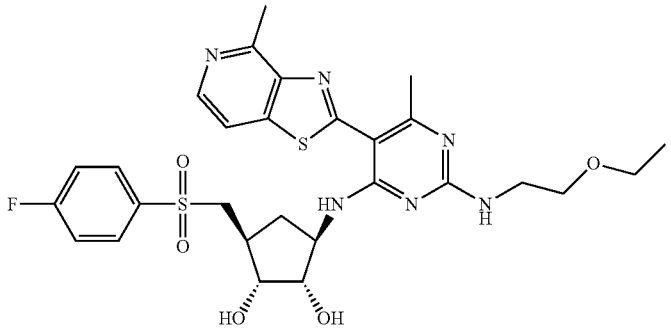
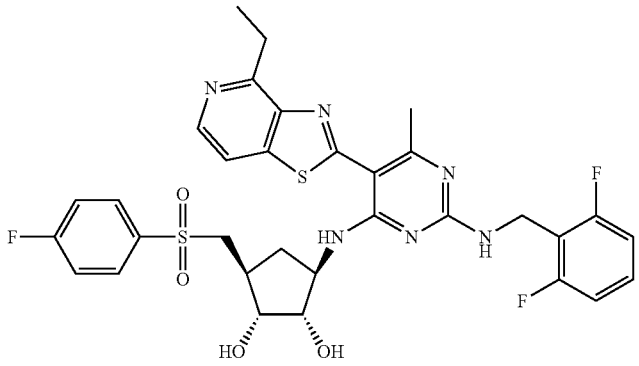
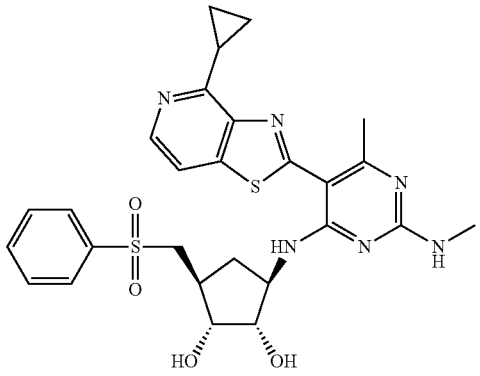
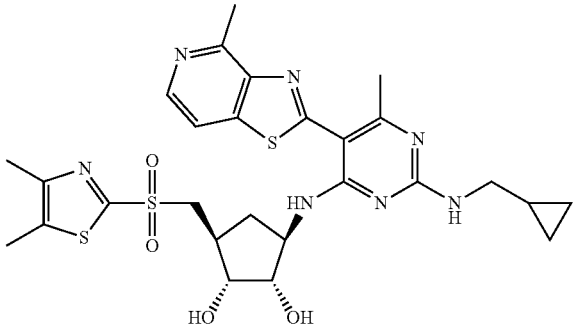
Compd #	Structure
3742	
3747	
3743	
3748	

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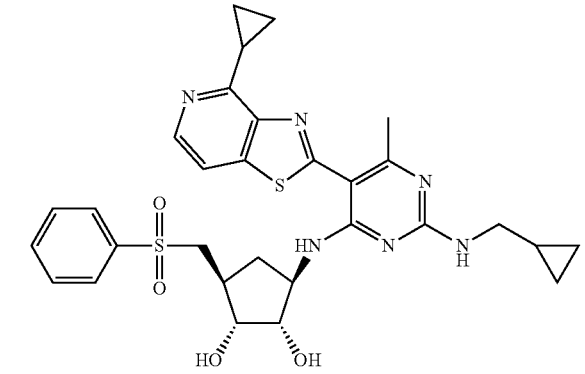
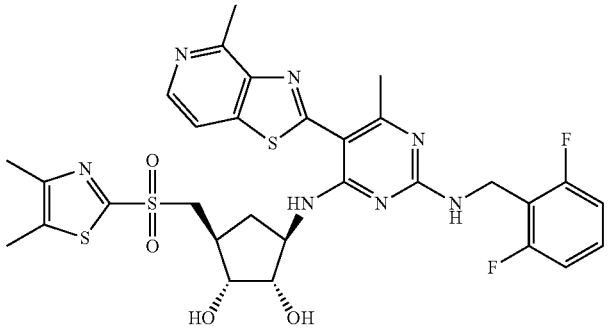
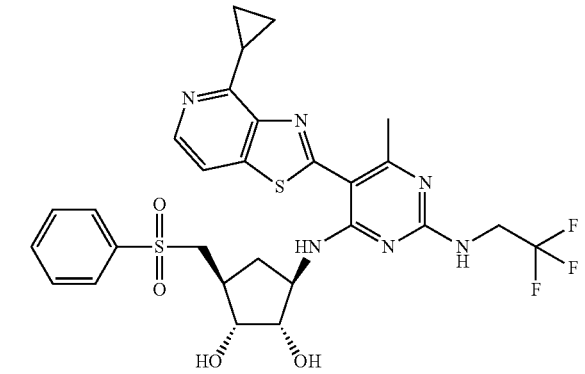
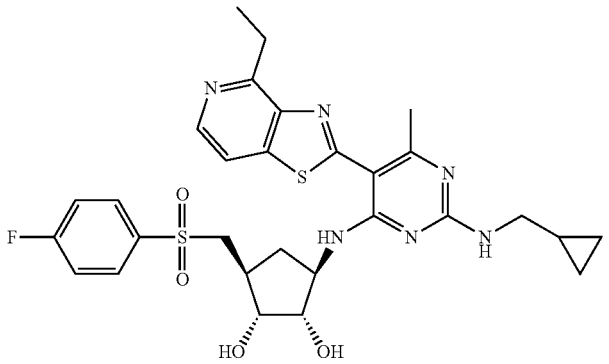
Compd #	Structure
3744	
3749	
3745	
3750	

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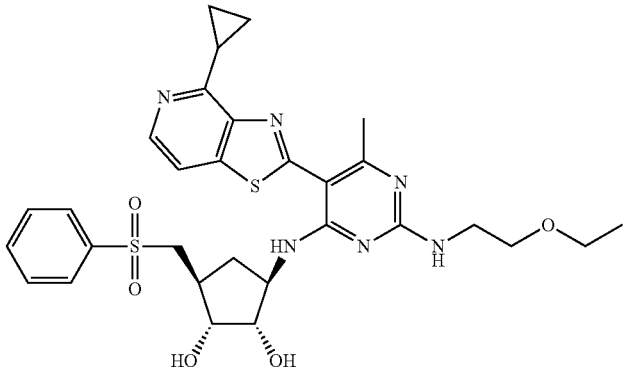
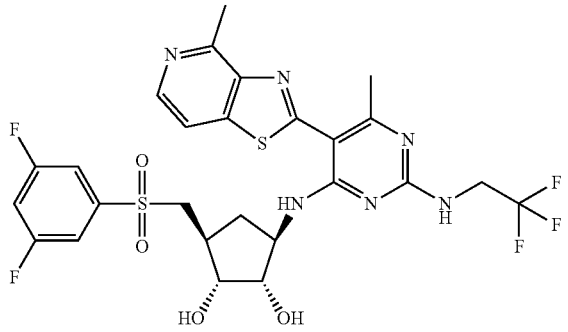
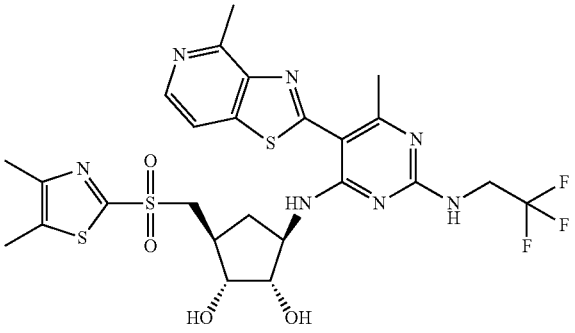
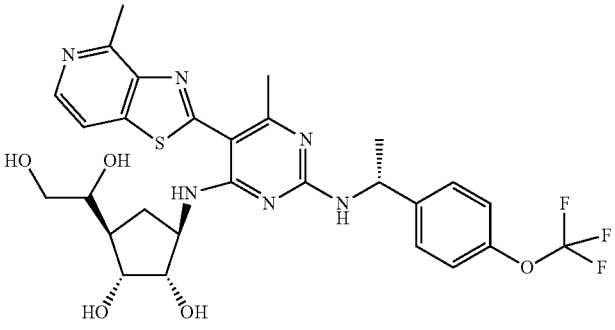
Compd #	Structure
3746	
3751	
3752	
3758	

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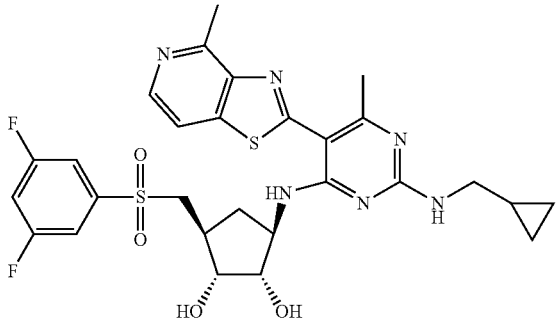
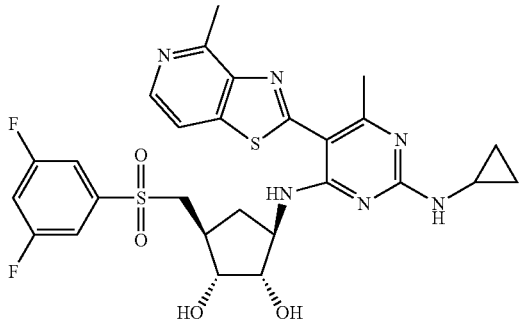
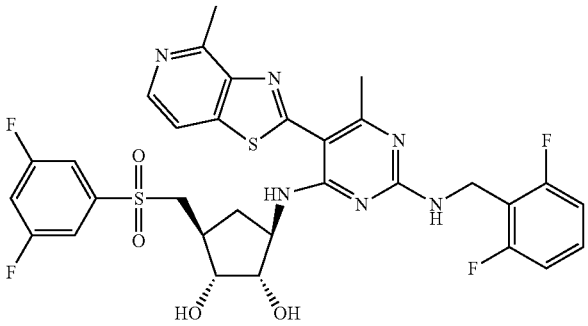
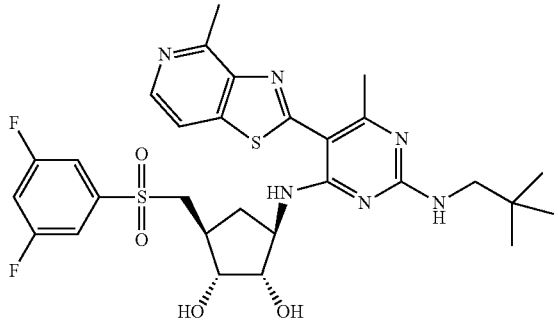
Compd #	Structure
3753	
3759	
3754	
3760	

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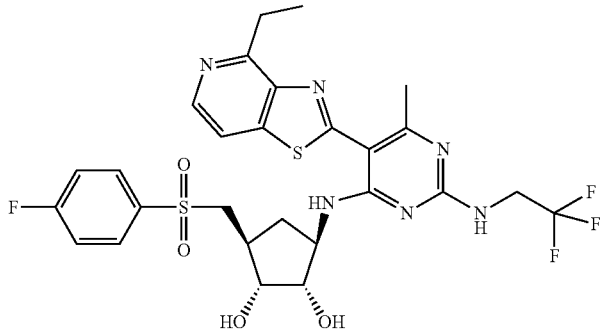
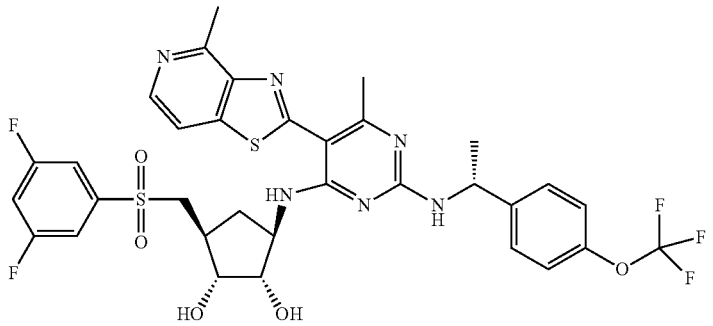
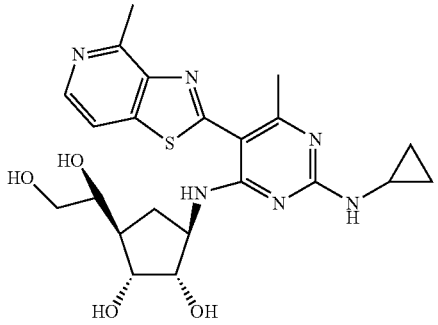
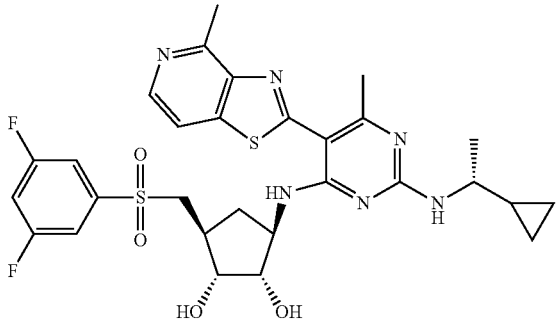
Compd #	Structure
3755	
3761	
3756	
3762	

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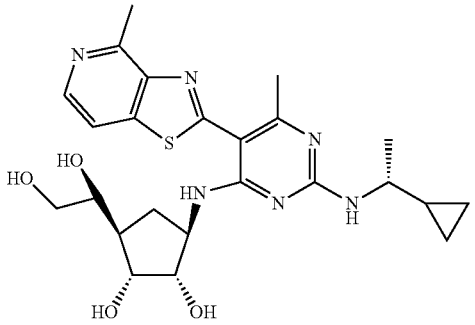
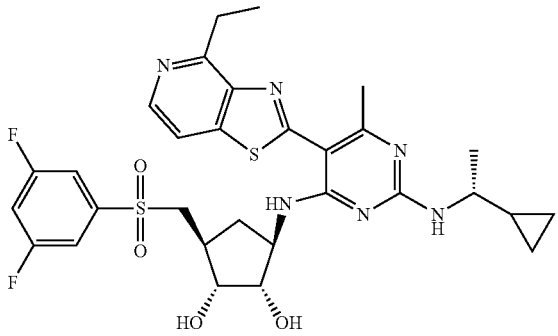
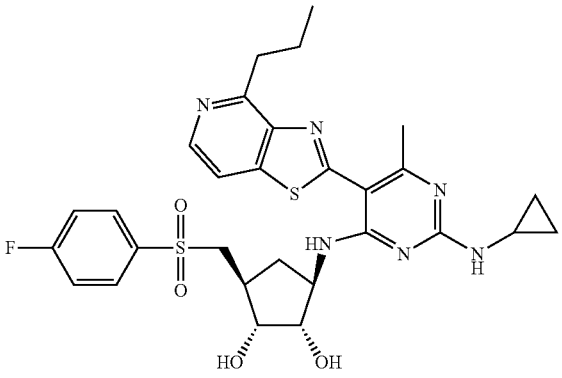
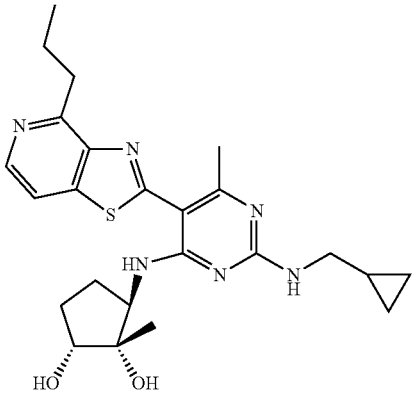
Compd #	Structure
3757	
3763	
3764	
3802	

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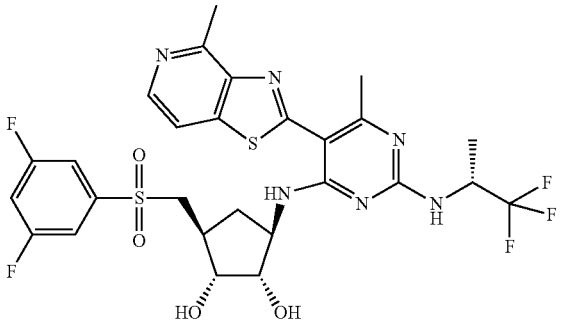
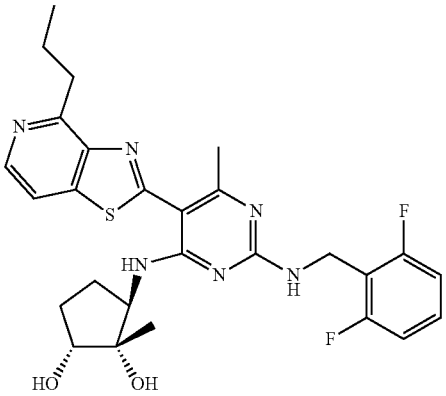
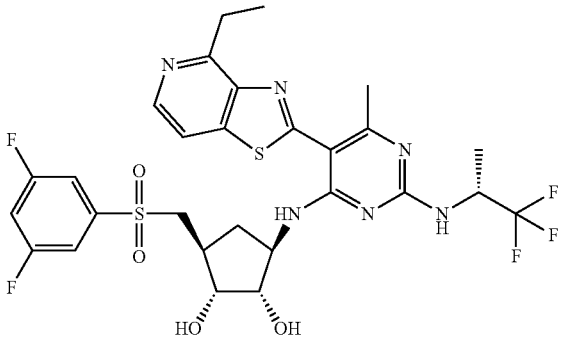
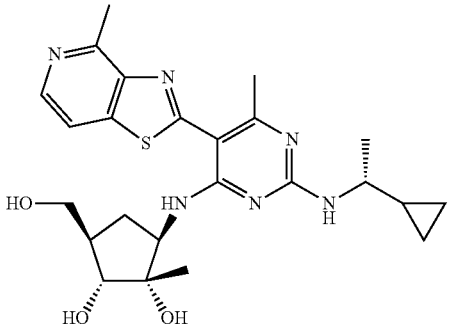
Compd #	Structure
3765	
3803	
3766	
3804	

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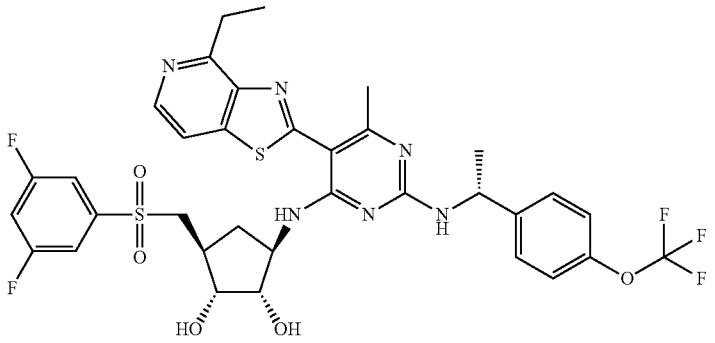
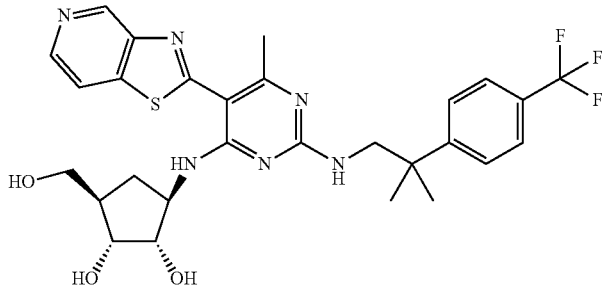
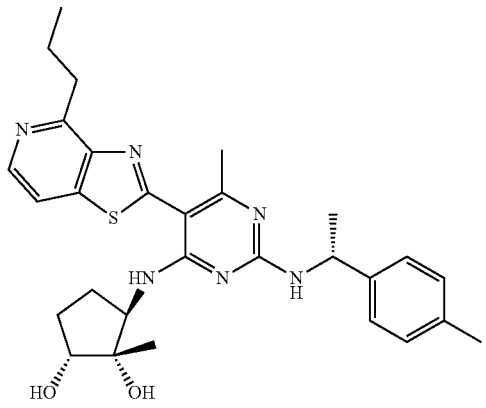
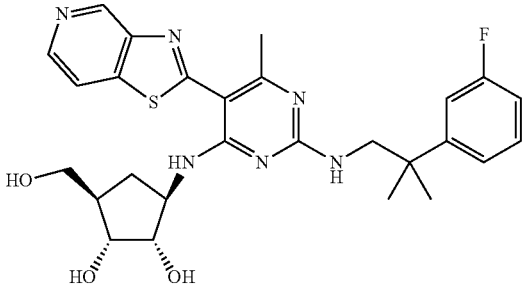
Compd #	Structure
3767	
3806	
3801	
3807	

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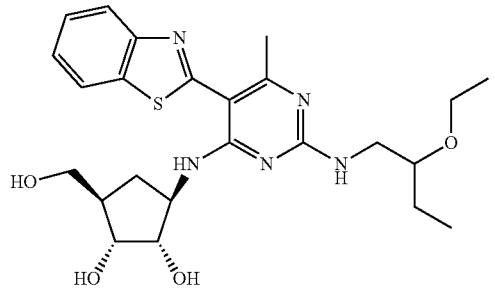
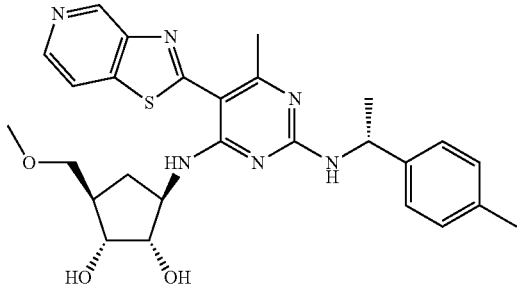
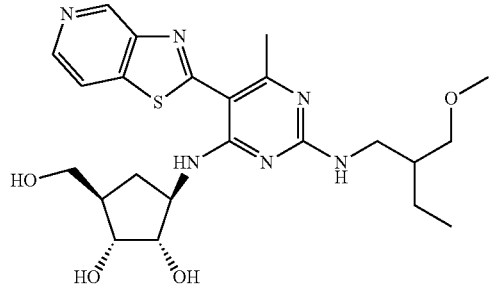
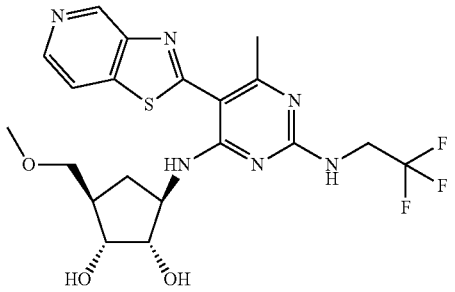
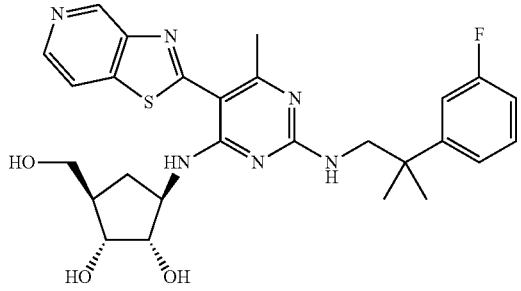
Compd #	Structure
3808	
3814A	
3809	
3814B	
3810	

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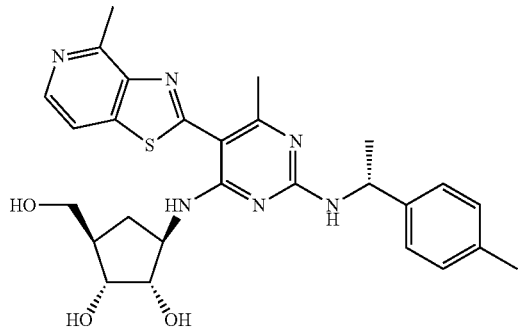
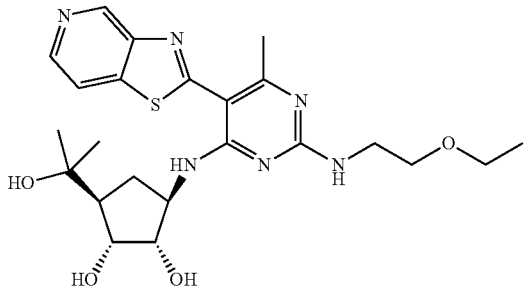
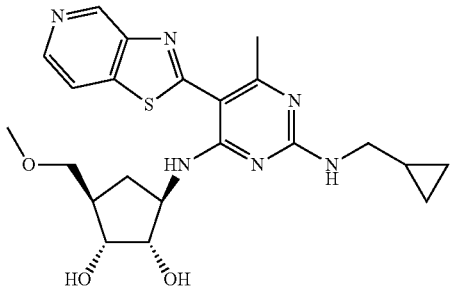
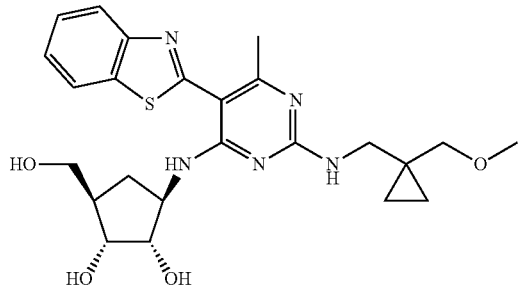
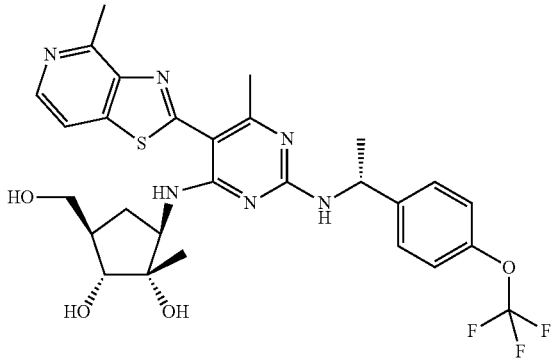
Compd #	Structure
3815A	
3811	
3815B	
3812	
3816	

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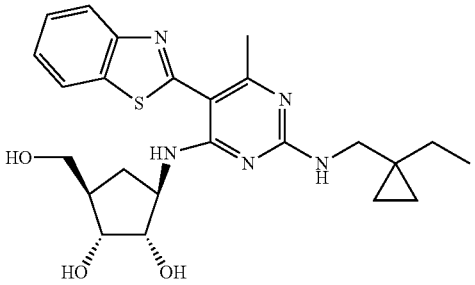
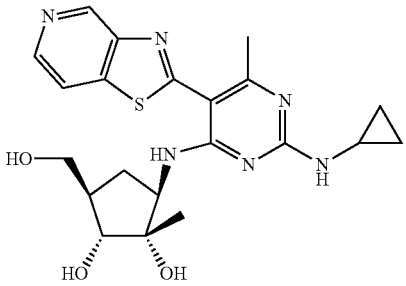
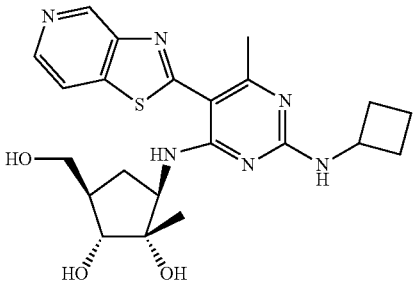
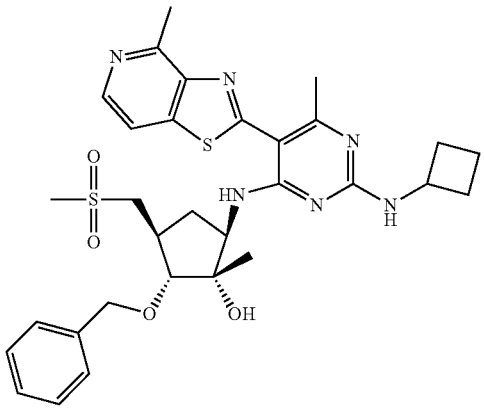
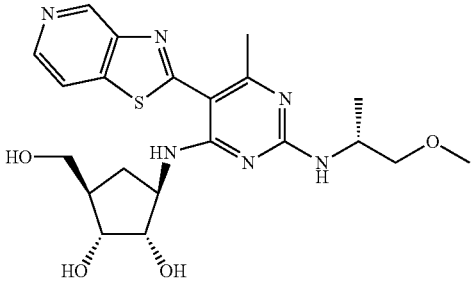
Compd #	Structure
3813	
3817	
3818	
3823	
3819	

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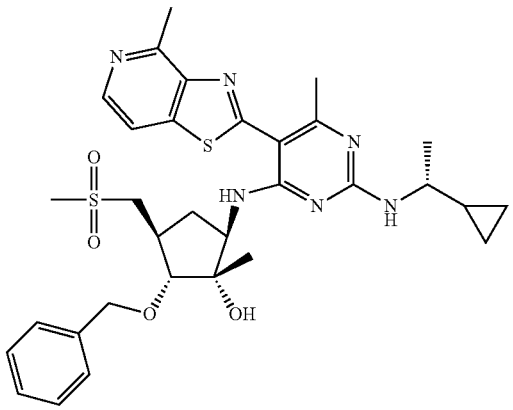
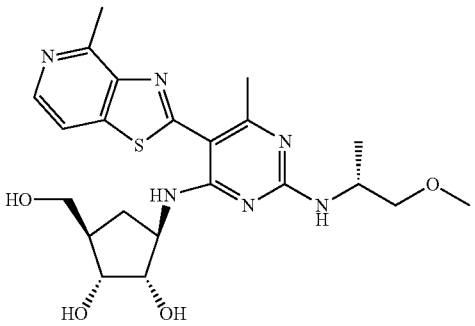
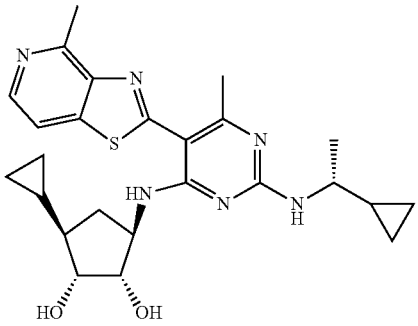
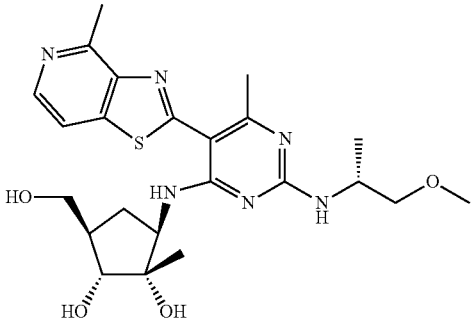
Compd #	Structure
3824	
3820	
3825	
3821	

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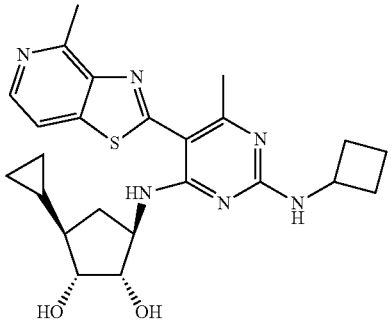
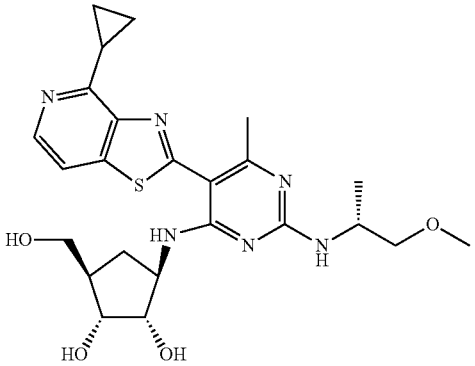
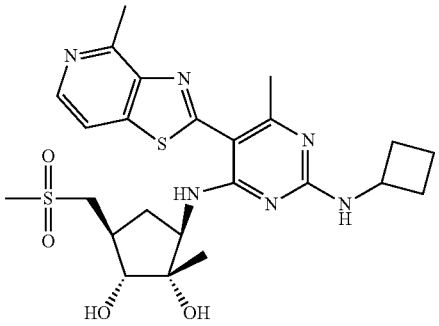
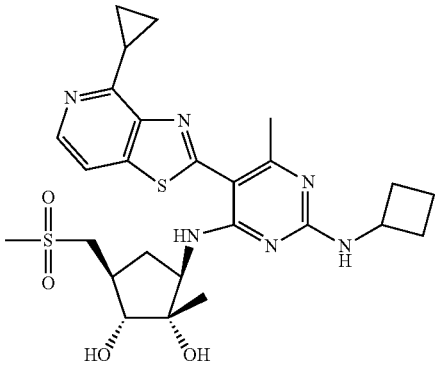
Compd #	Structure
3826	
3822	
3827	
3830	

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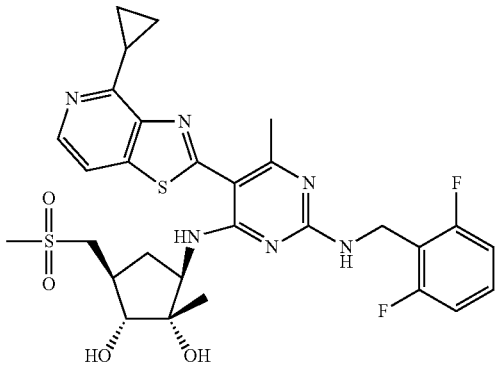
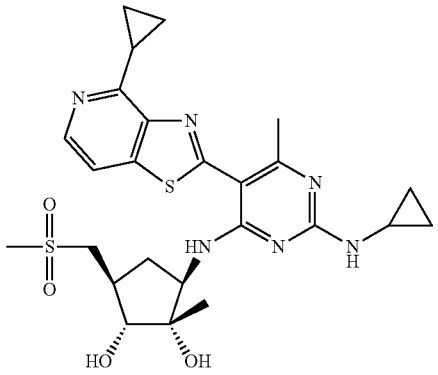
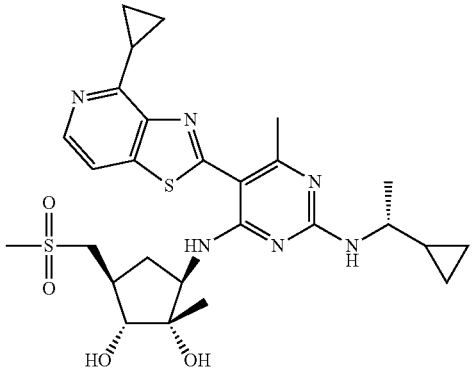
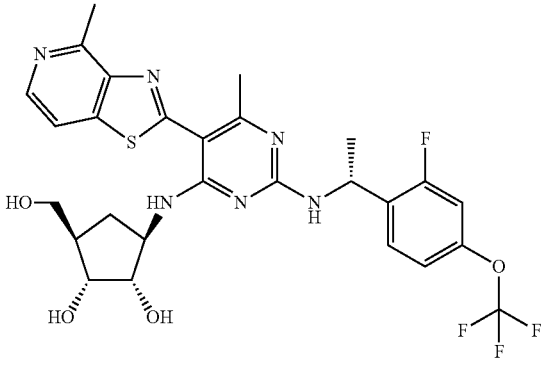
Compd #	Structure
3834	
3831	
3835	
3836	

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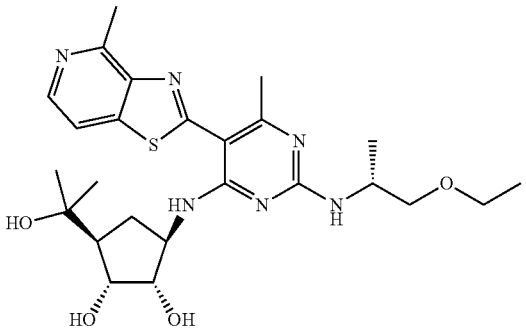
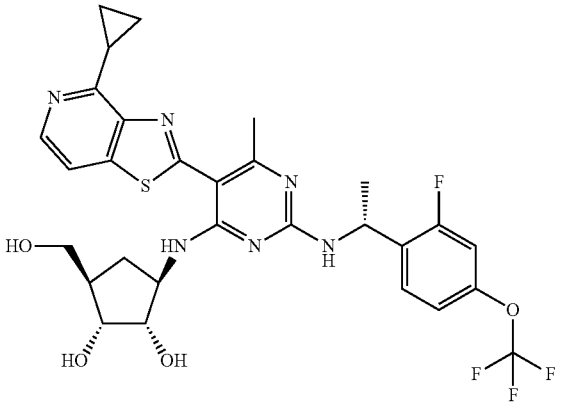
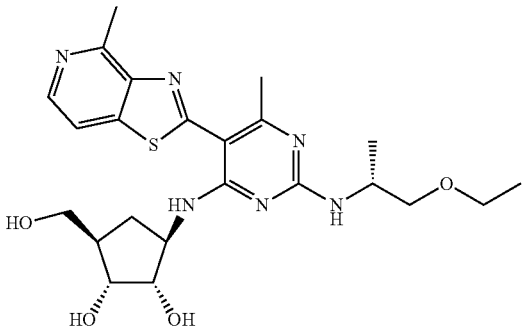
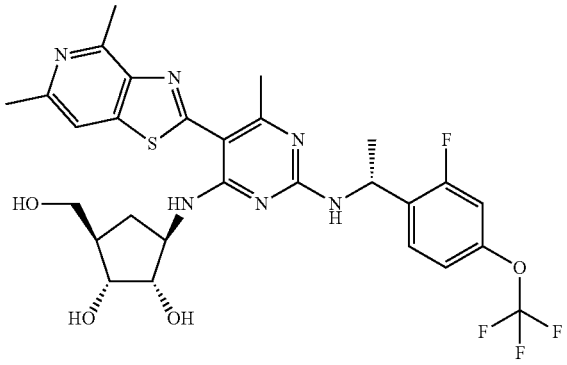
Compd #	Structure
3842	
3837	
3843	
3838	

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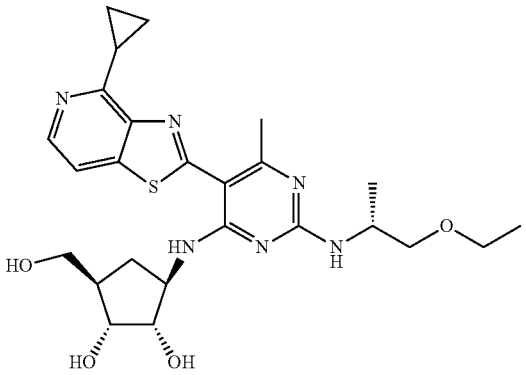
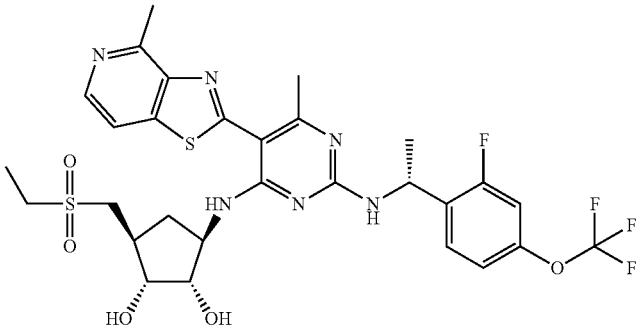
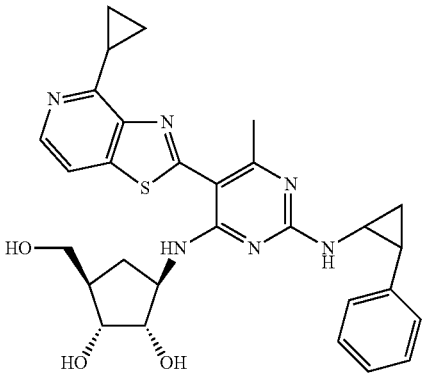
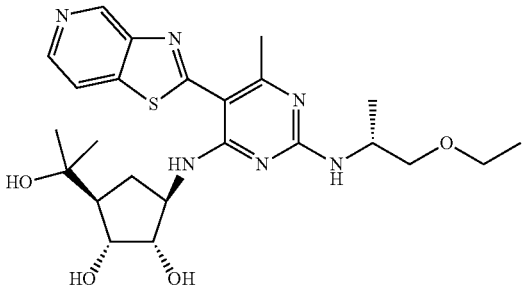
3844	
3840	
3845	
3841	

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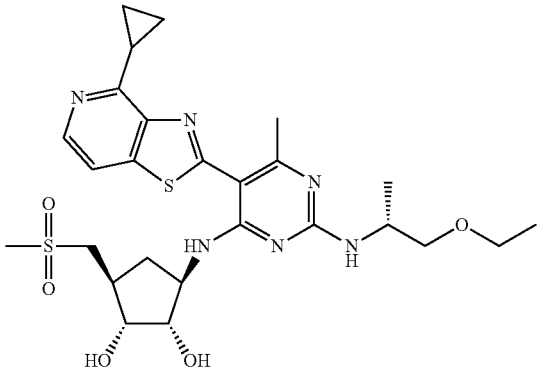
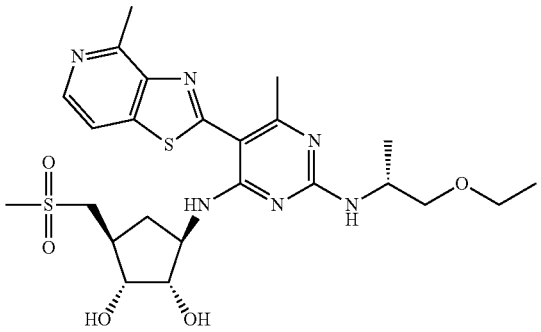
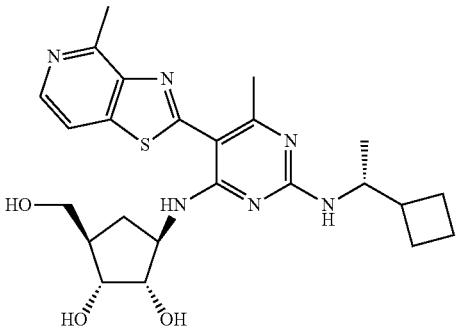
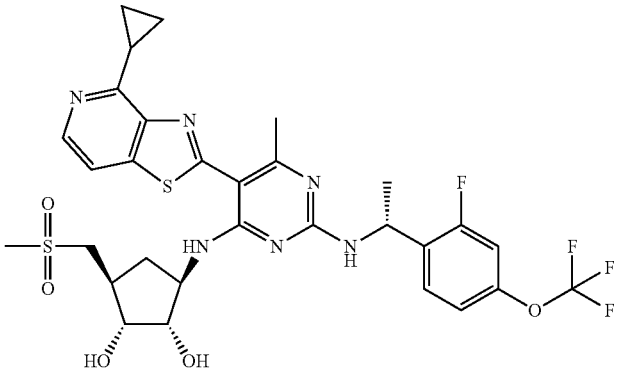
Compd #	Structure
3846	
3847	
3904	
3848	

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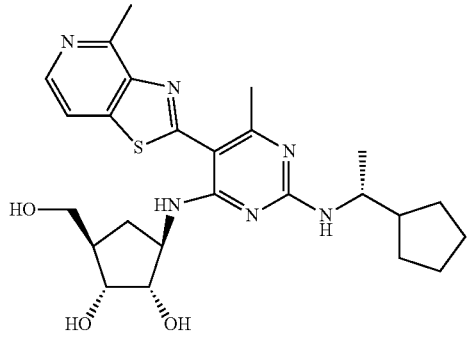
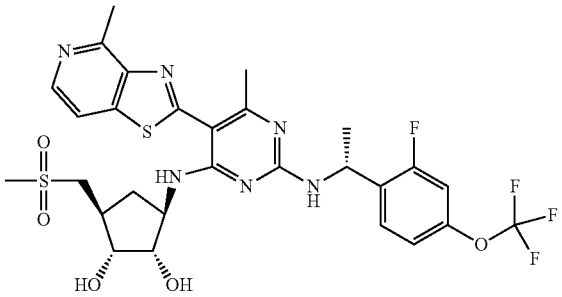
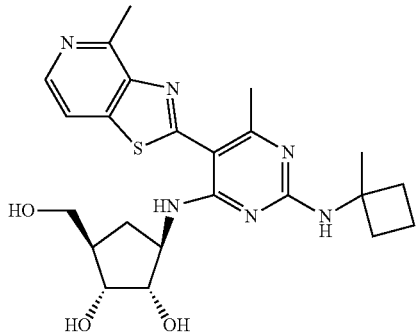
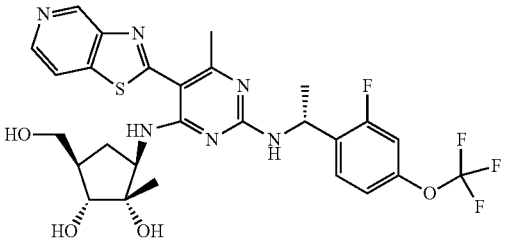
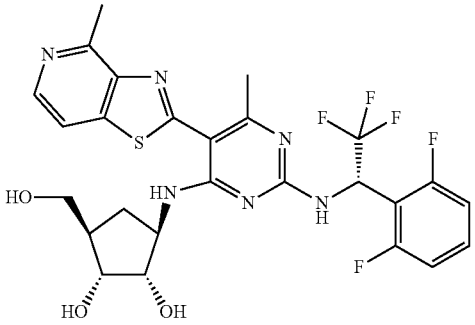
3905	
3849	
3906	
3850	
3907	

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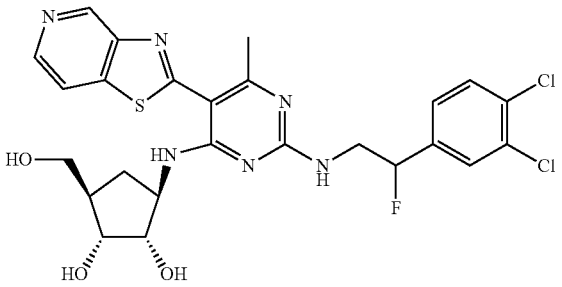
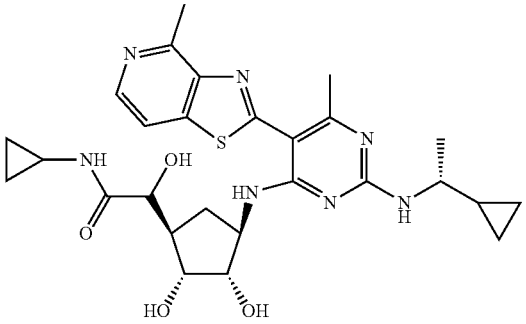
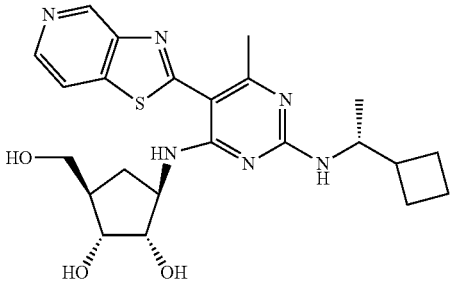
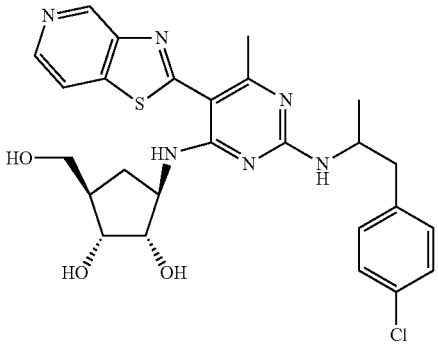
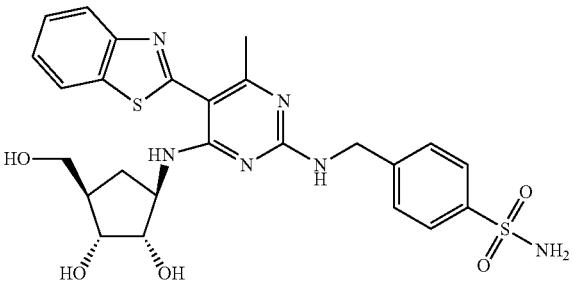
Compd #	Structure
3901	
3908	
3903	
4001	
4002	

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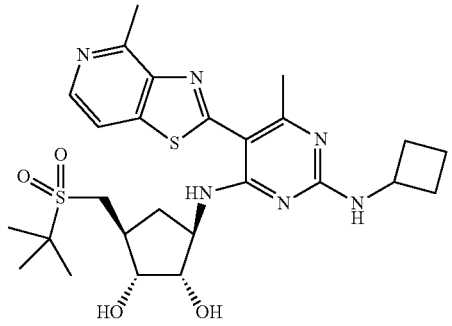
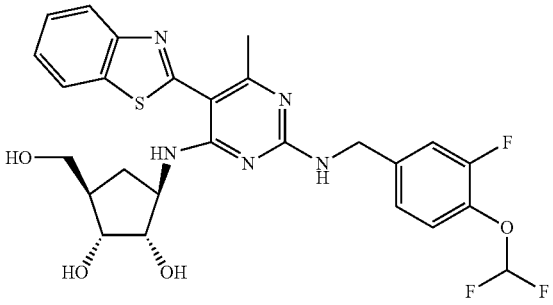
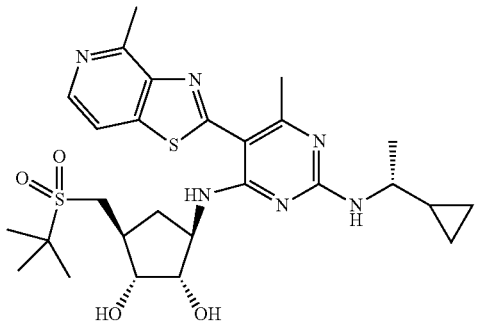
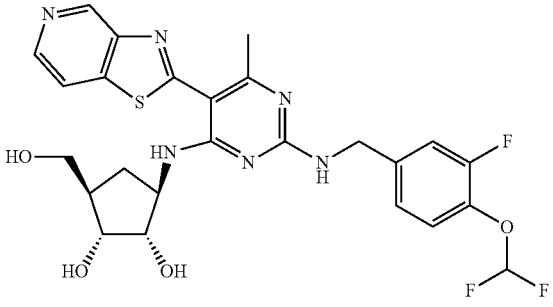
Compd #	Structure
4009	
4003	
4010	
4004	

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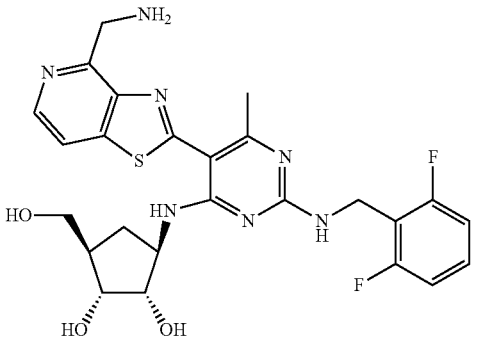
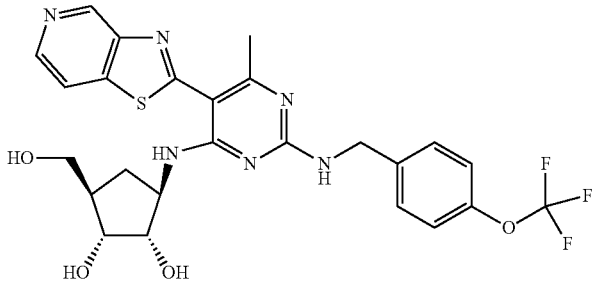
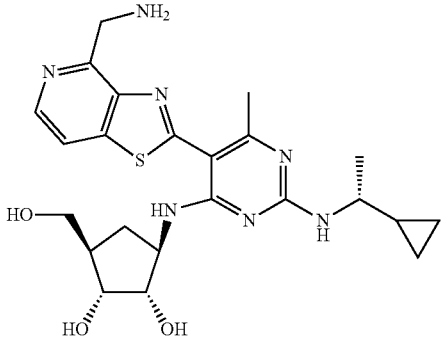
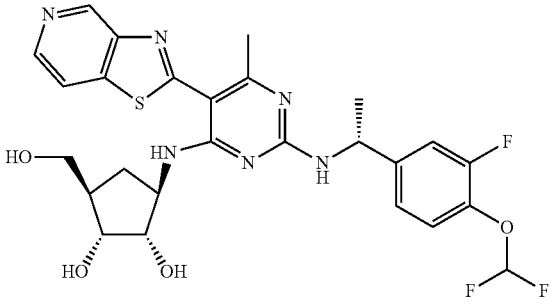
Compd #	Structure
4012	
4006	
4013	
4007	

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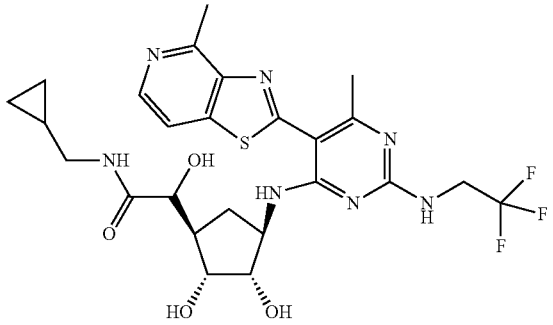
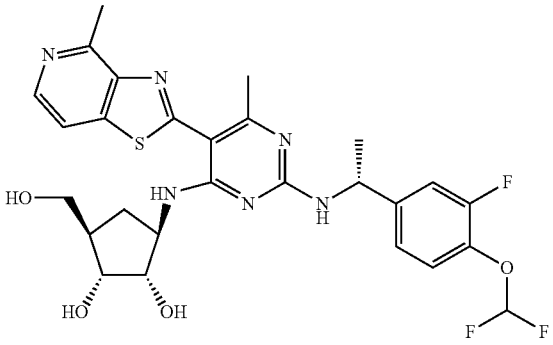
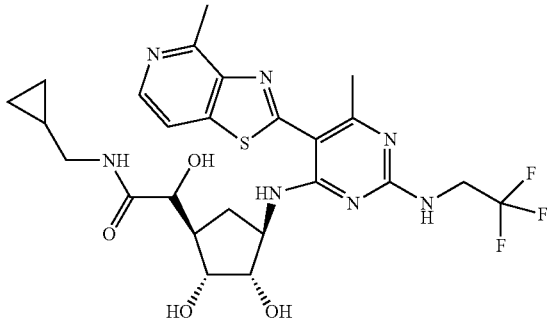
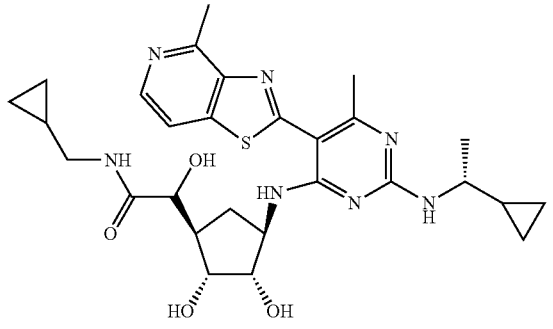
4014	
4008	
4015	
4016	

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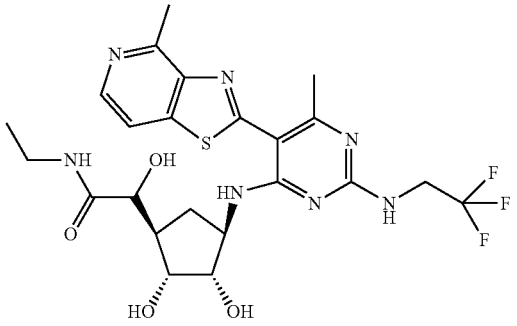
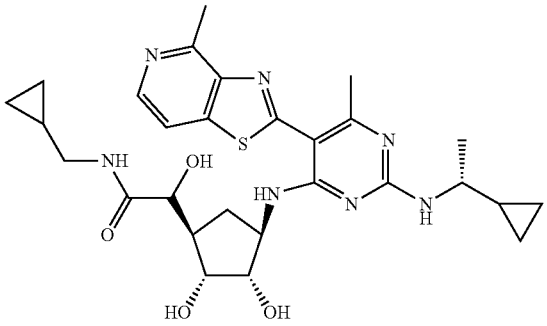
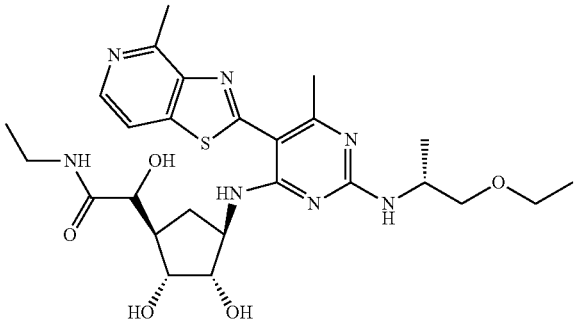
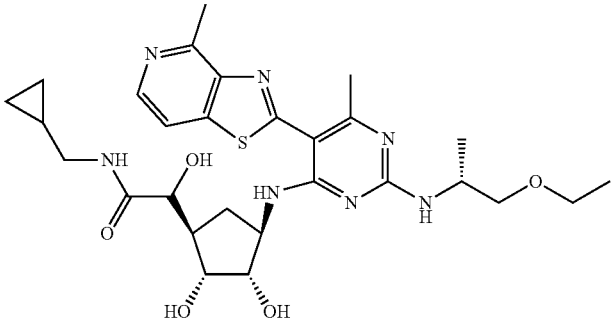
4023	
4017	
4024	
4018	

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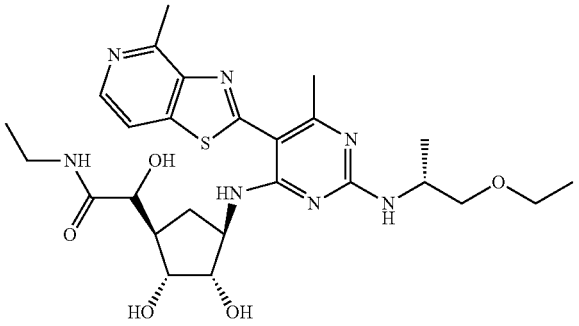
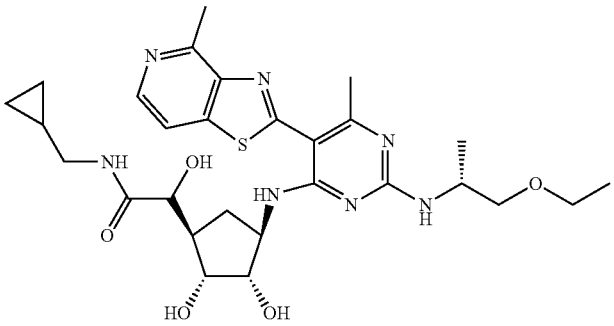
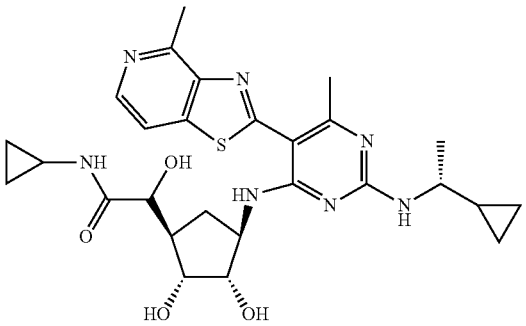
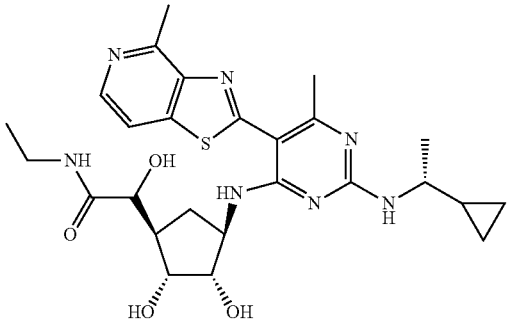
4025	
4019	
4026	
4020	

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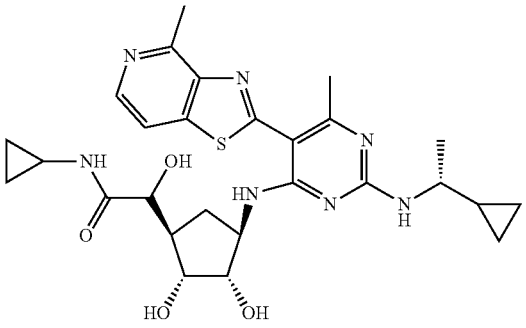
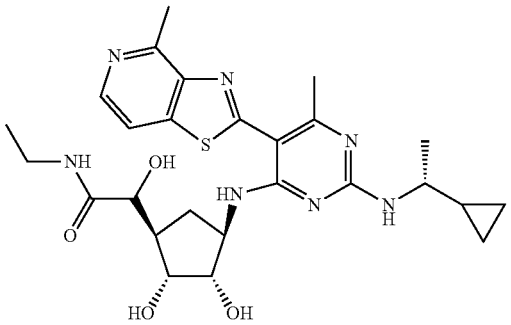
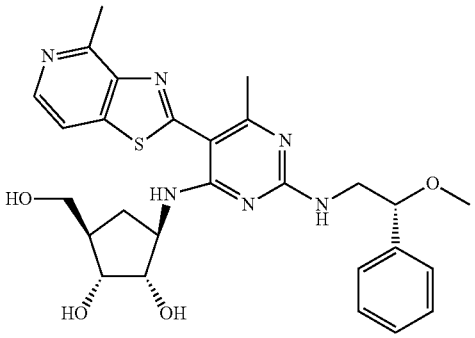
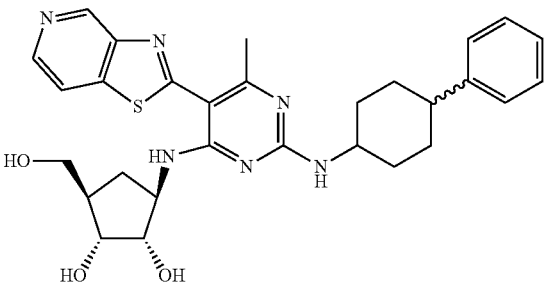
4027	
4021	
4028	
4105	

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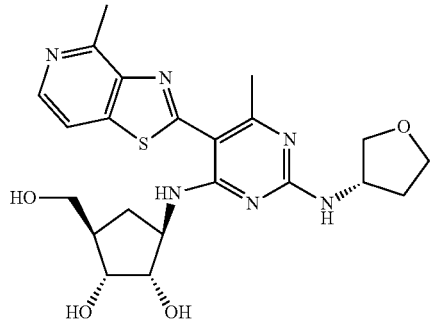
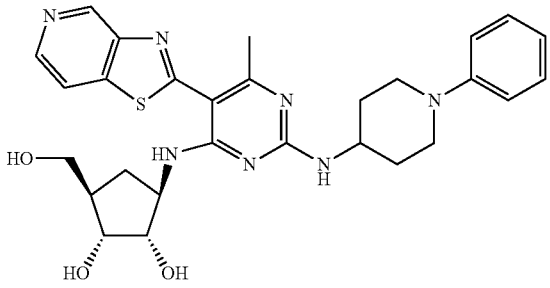
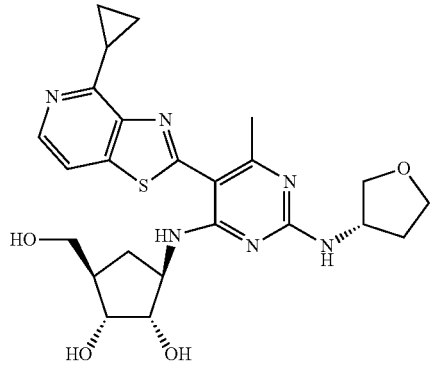
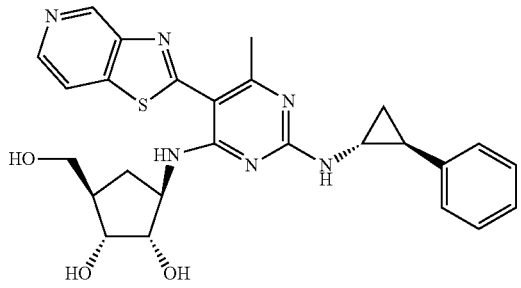
4116	
4106	
4117	
4107	

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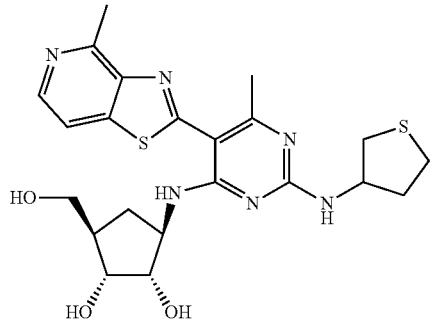
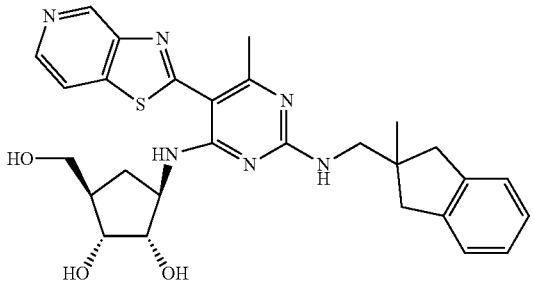
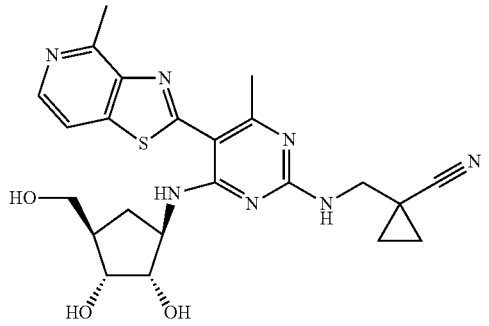
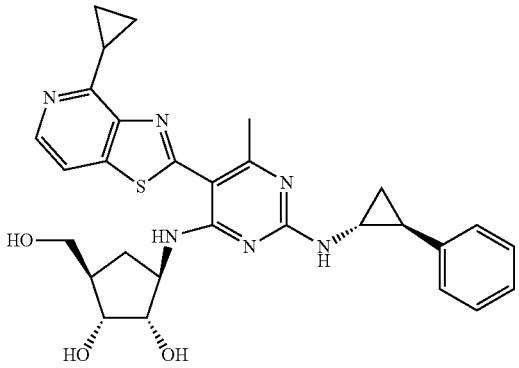
4119	
4109	
4120	
4114	

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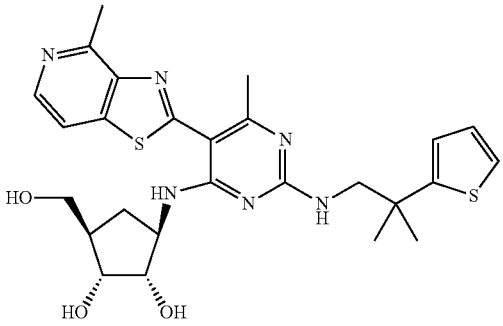
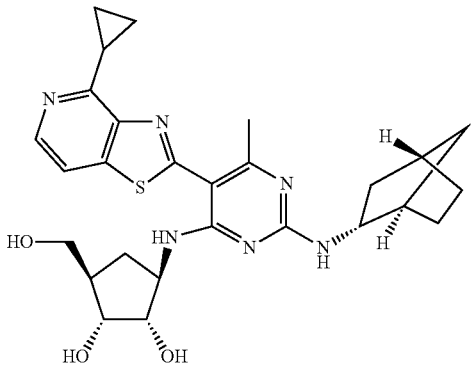
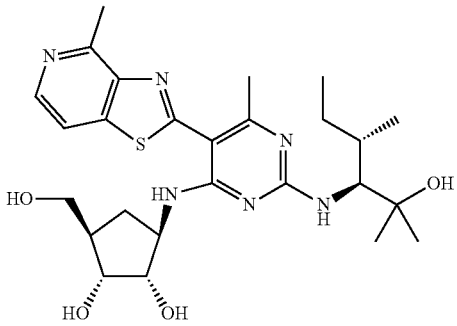
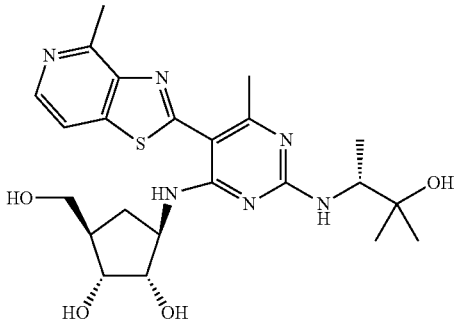
4121	
4115	
4122	
4123	

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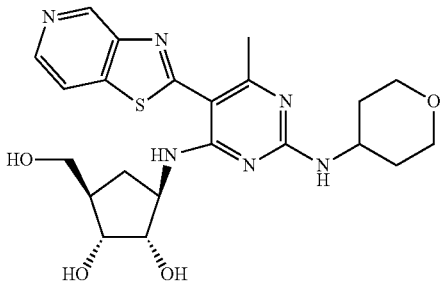
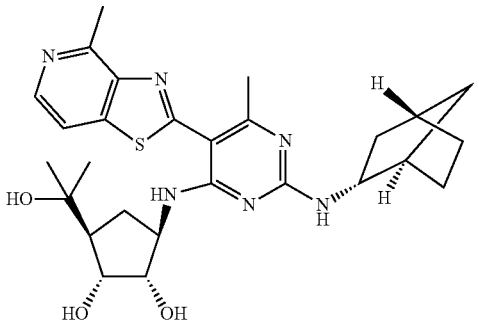
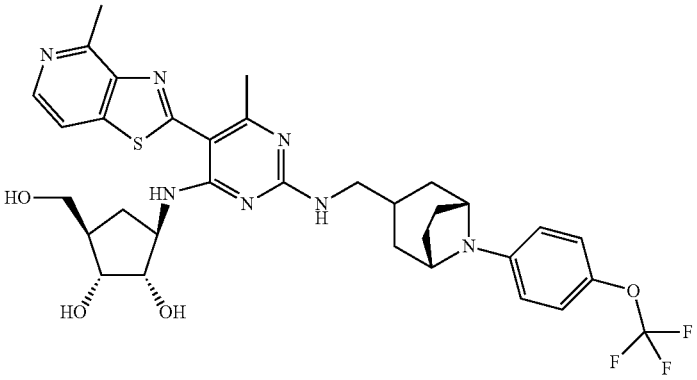
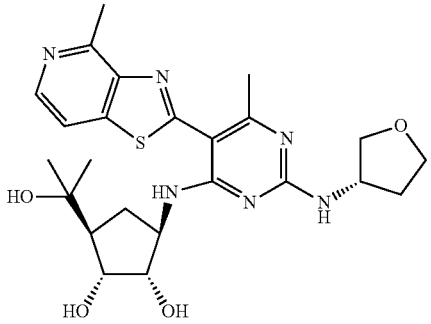
4204	
4125	
4205	
4126	

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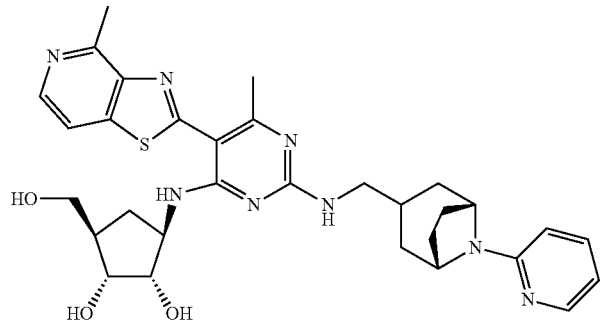
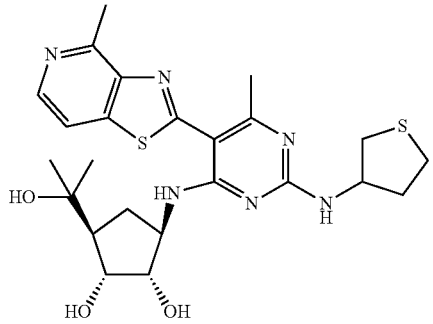
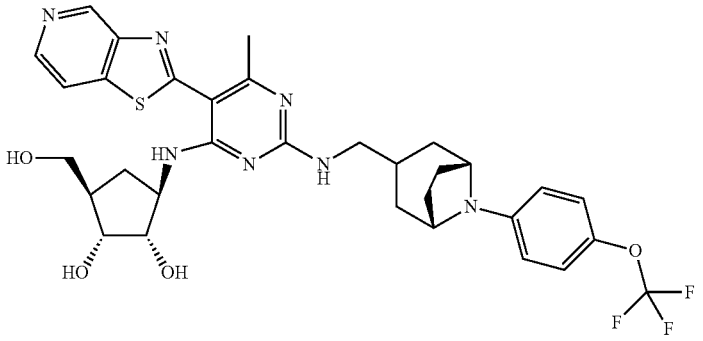
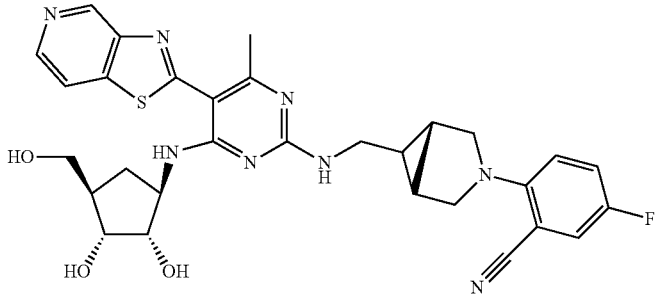
4206	
4127	
4207	
4203	

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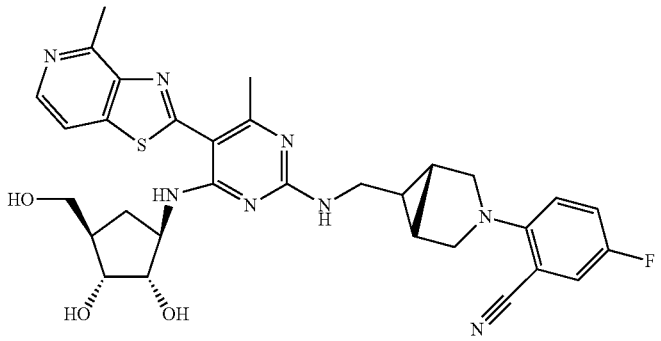
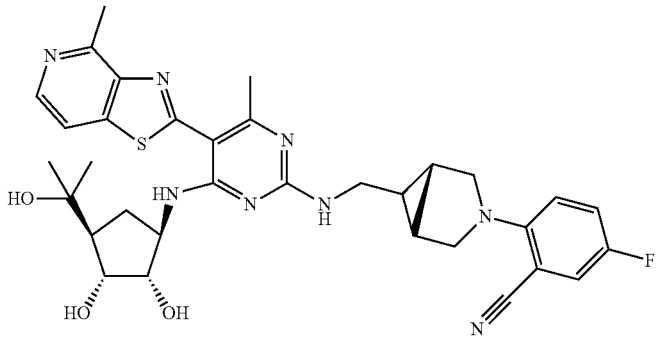
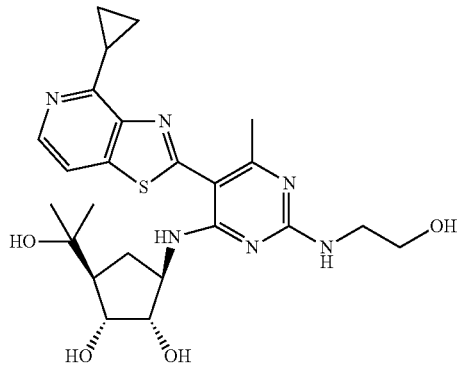
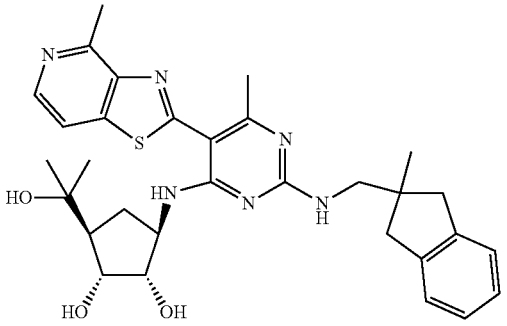
4208	
4210	
4220	
4211	

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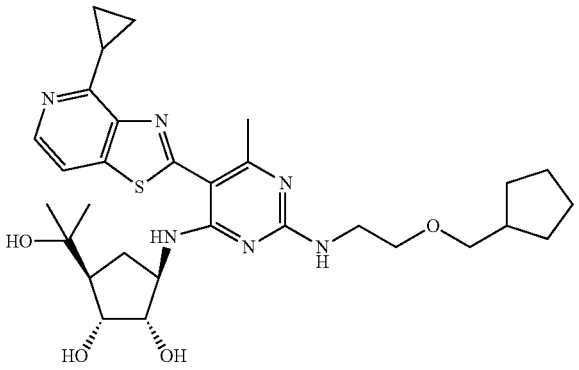
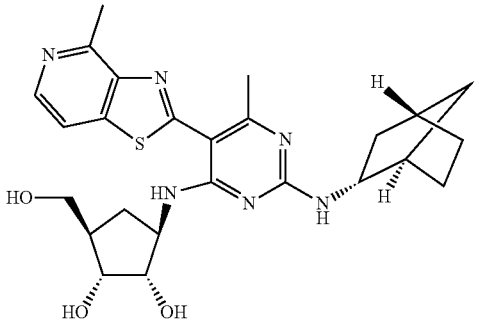
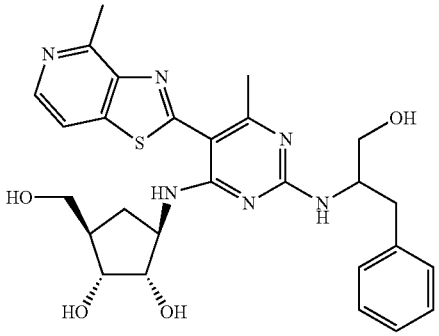
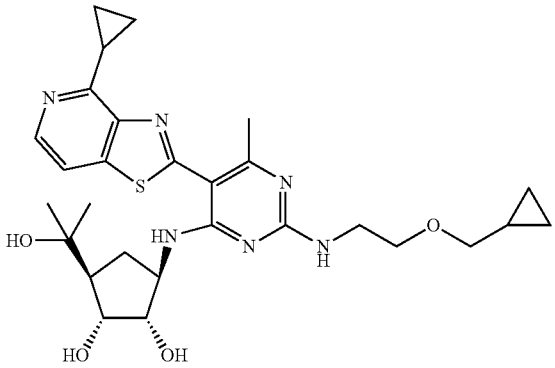
4221	
4212	
4223	
4213	

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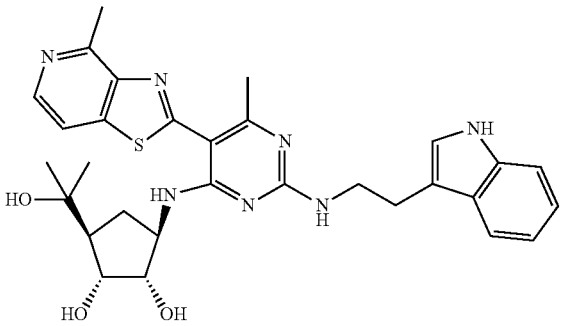
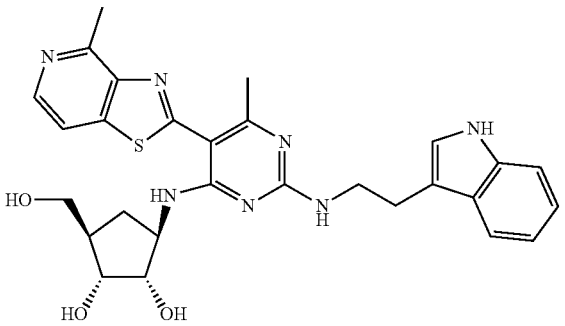
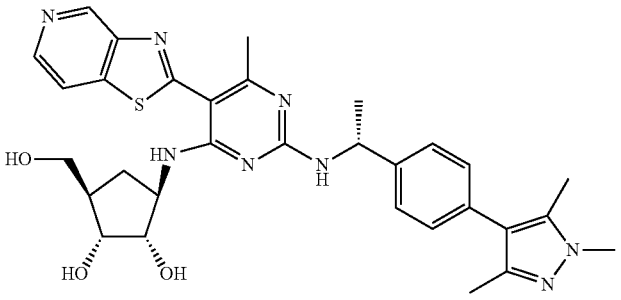
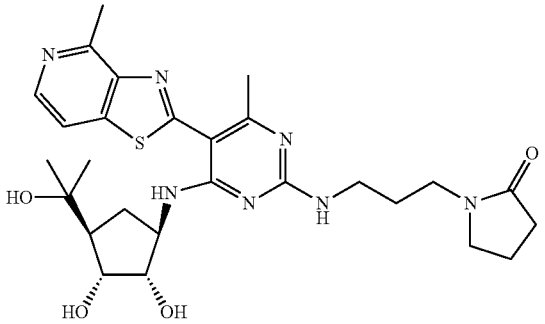
4227	
4217	
4304	
4229	

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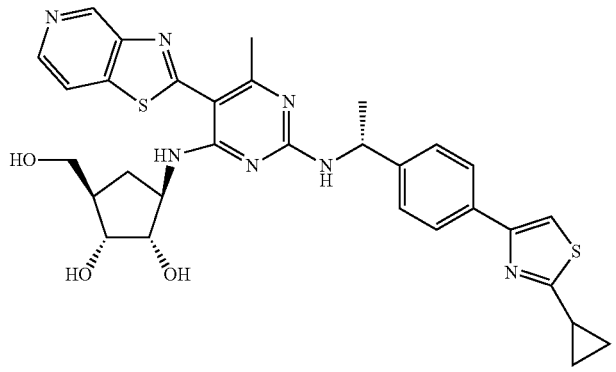
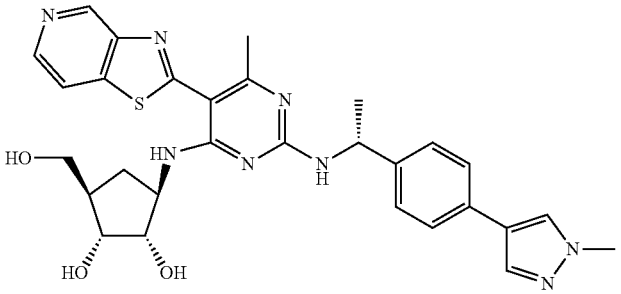
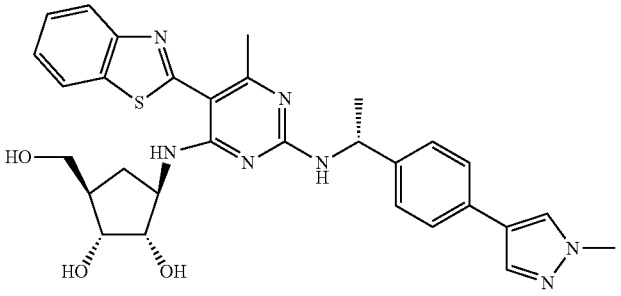
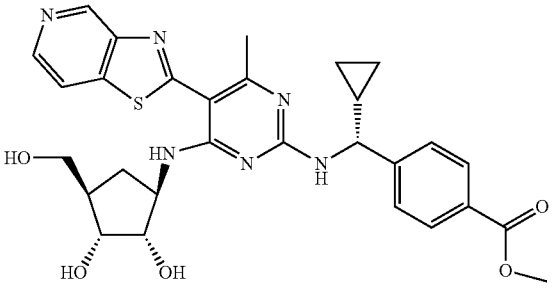
4305	
4301	
4306	
4302	

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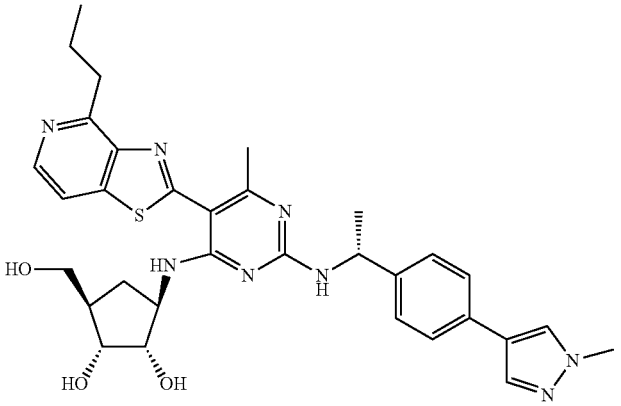
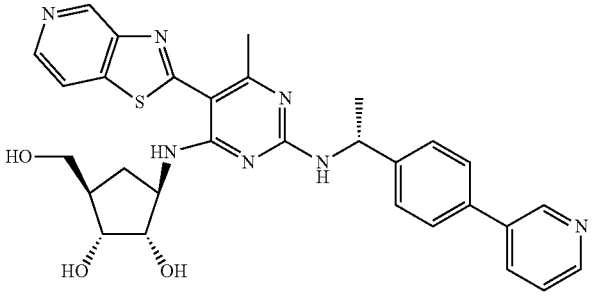
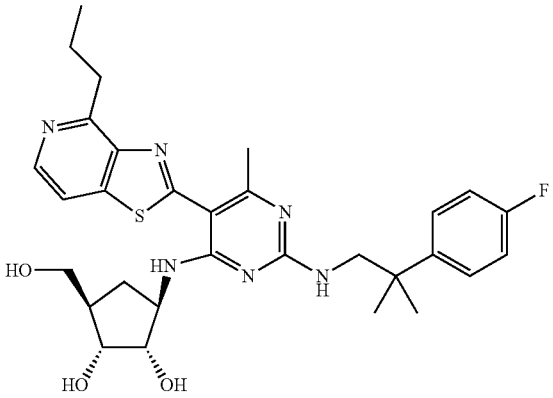
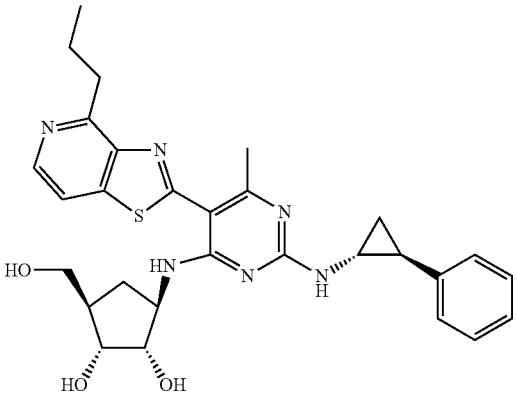
Compd #	Structure
4307	
4303	
4308	
4309	

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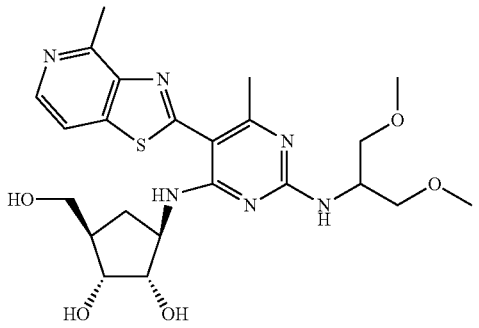
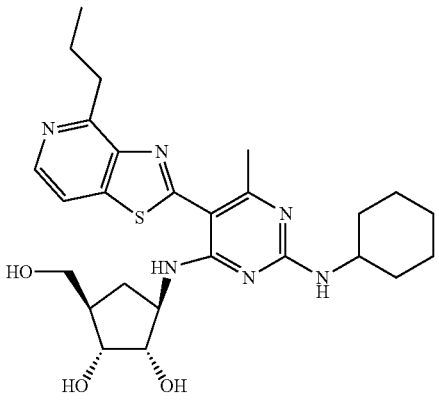
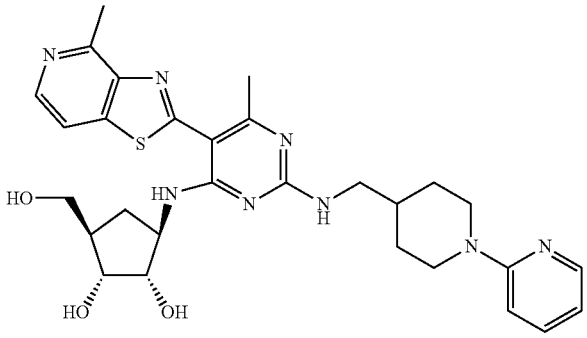
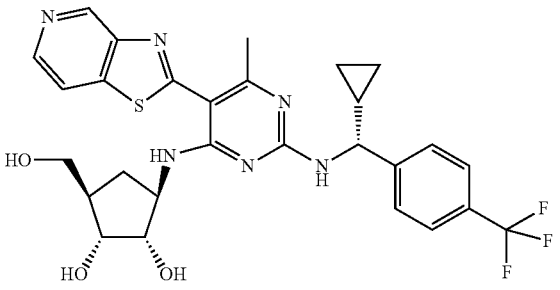
4320	
4310	
4321	
4311	

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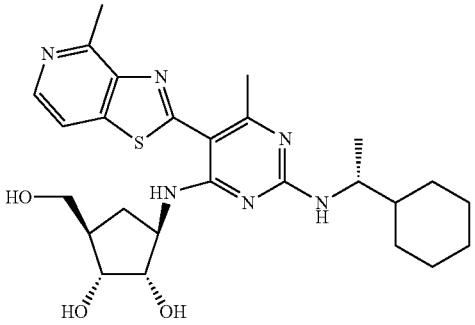
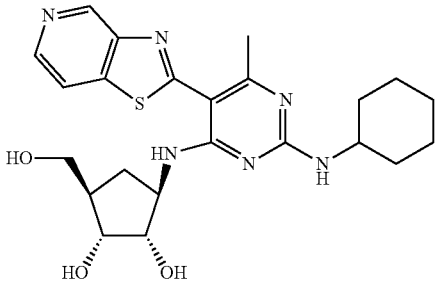
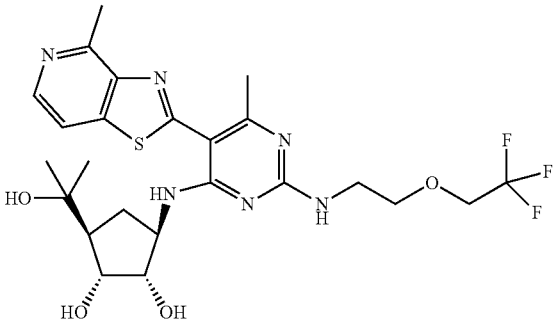
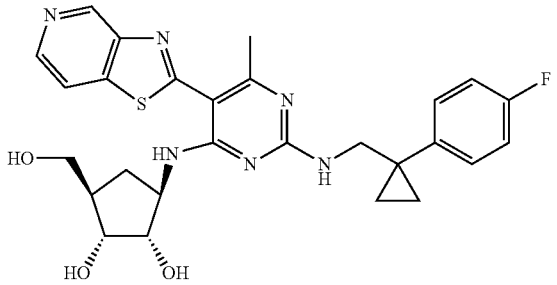
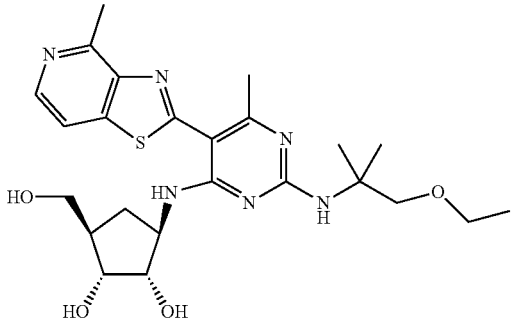
4322	
4312	
4323	
4316	
4324	

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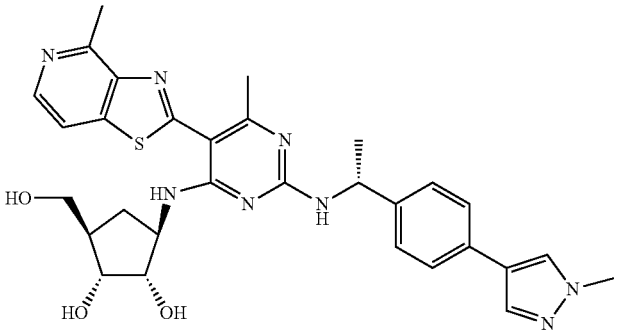
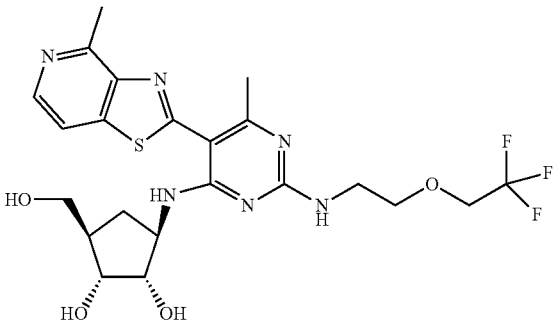
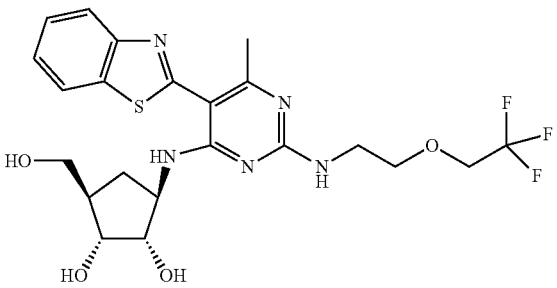
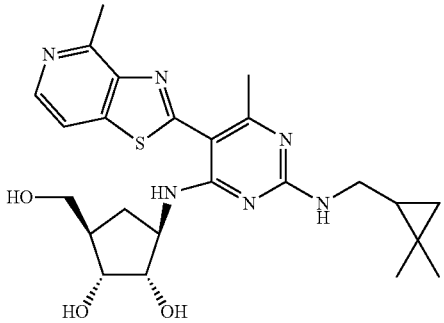
4319	
4325	
4326	
4332	

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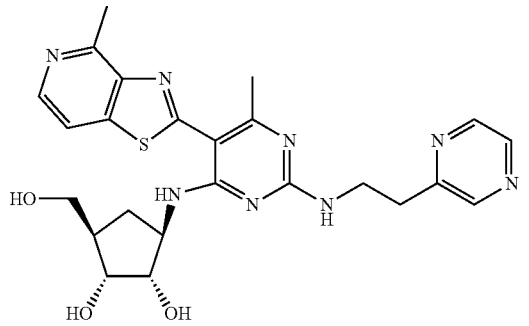
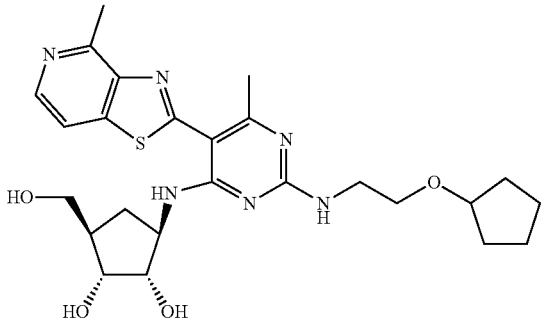
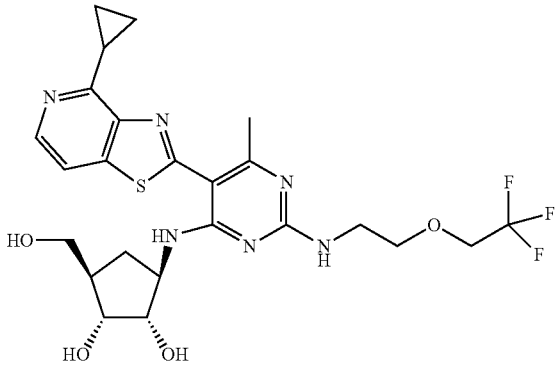
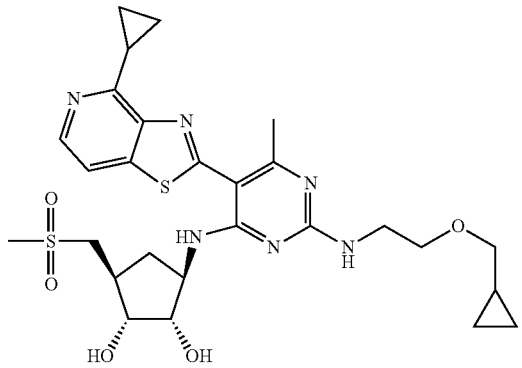
Compd #	Structure
4327	
4333	
4328	
4334	

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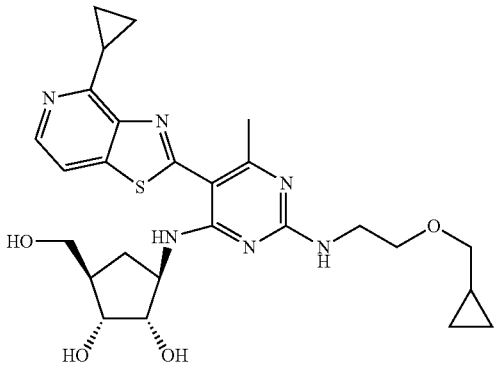
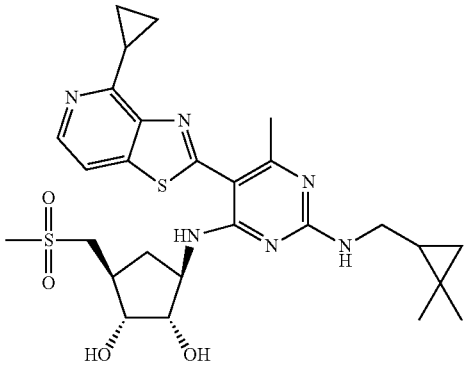
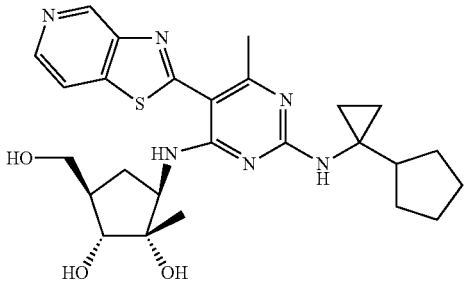
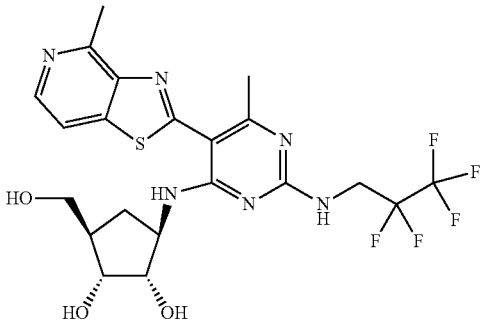
4329	
4335	
4330	
4336	

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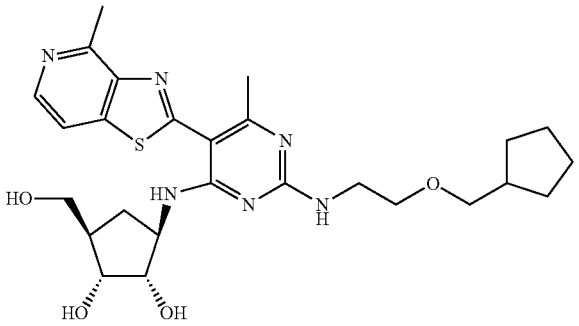
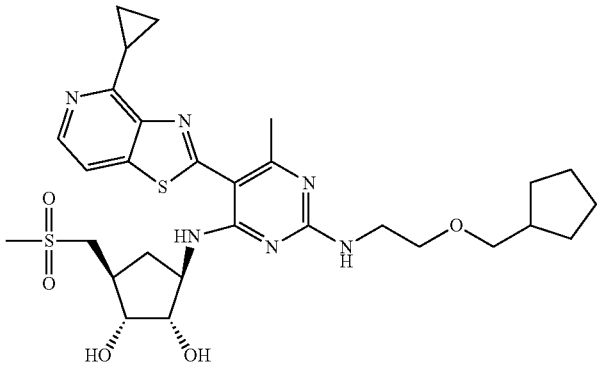
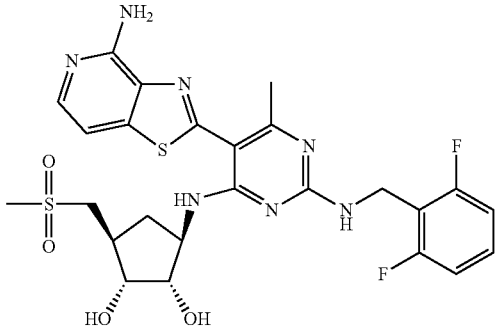
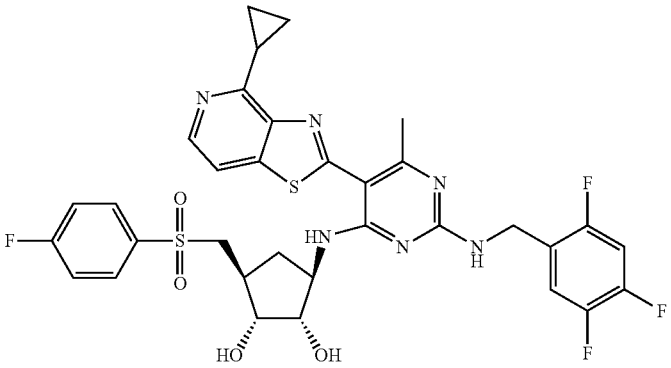
4331	
4337	
4338	
4343	

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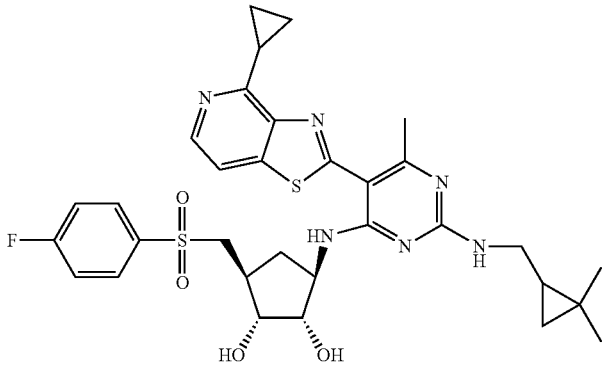
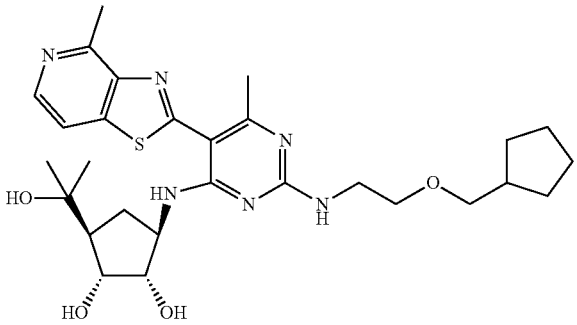
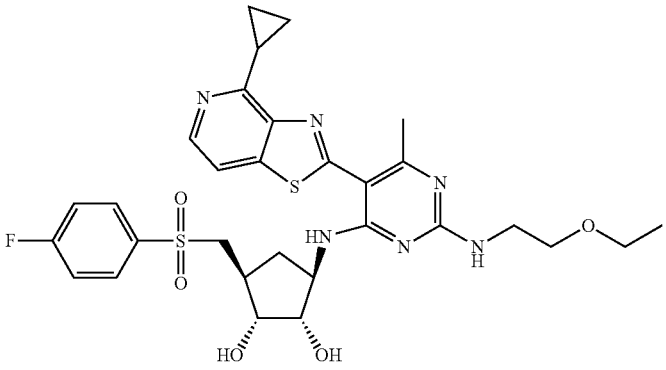
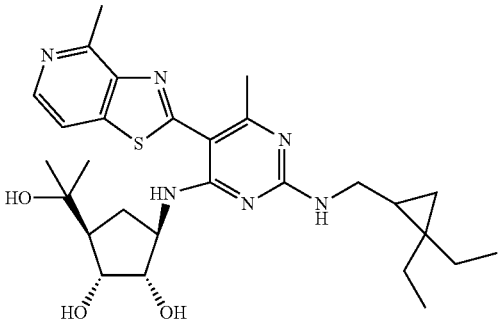
4339	
4344	
4340	
4345	

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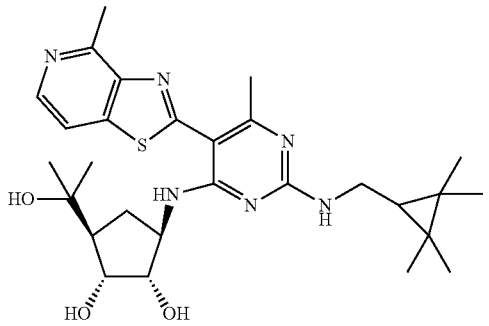
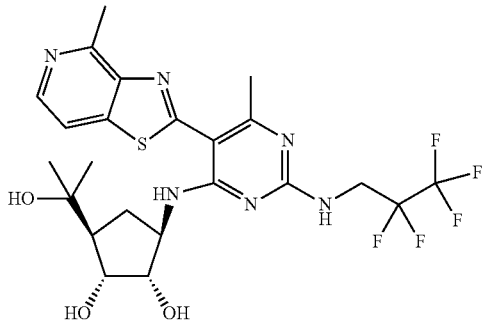
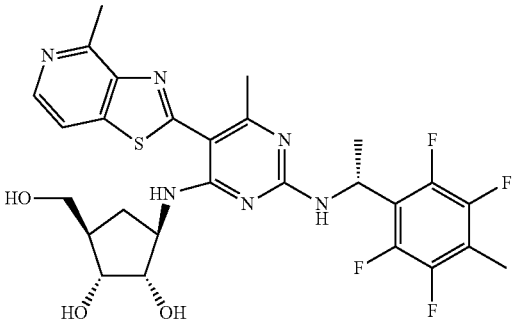
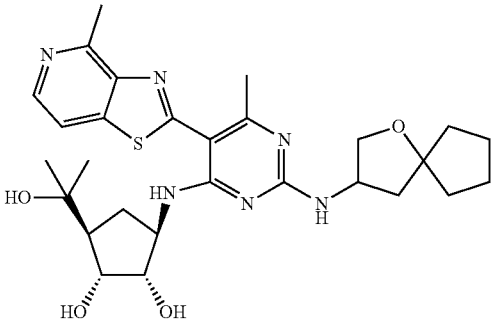
4341	
4346	
4342	
4347	

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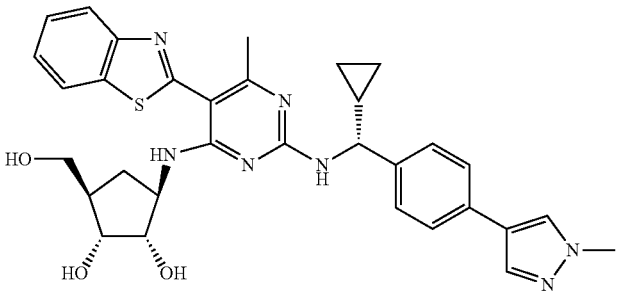
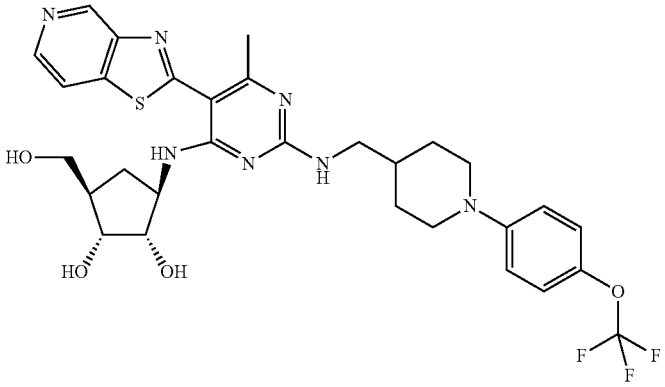
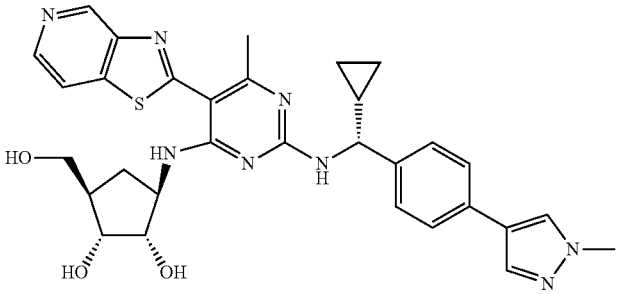
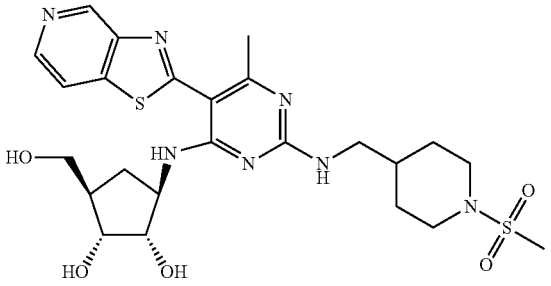
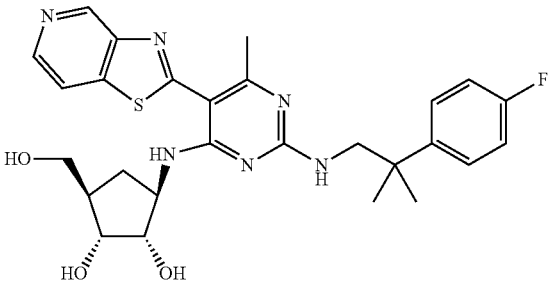
4404	
4411	
4405	
4412	
4406	

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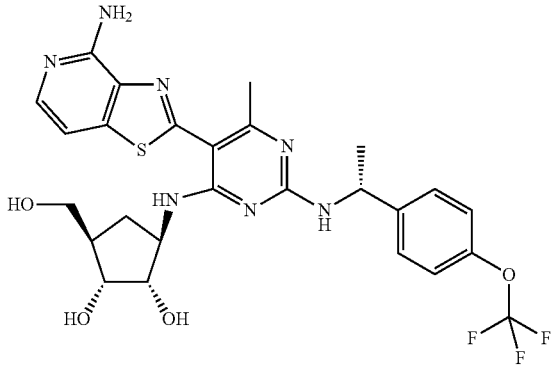
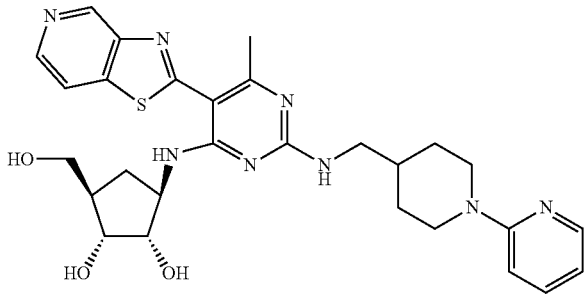
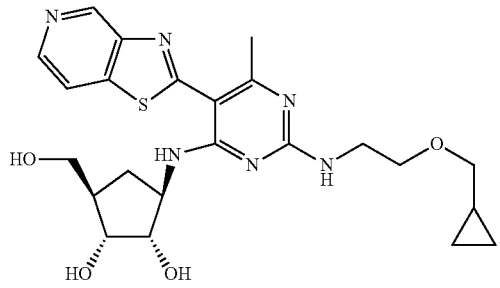
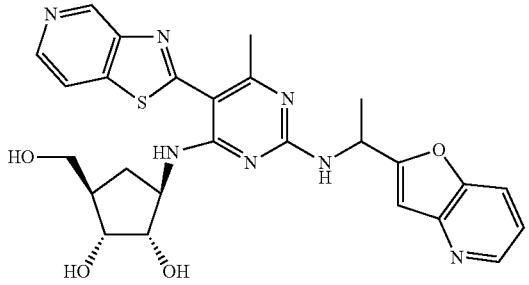
4413	
4407	
4414	
4409	

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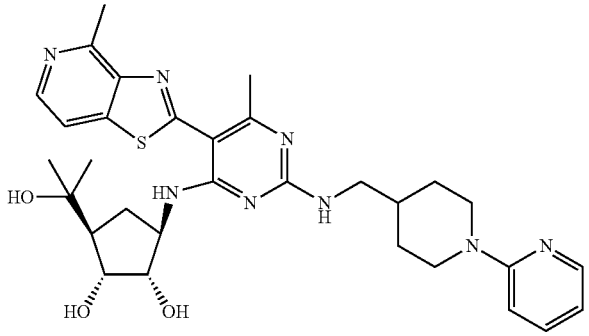
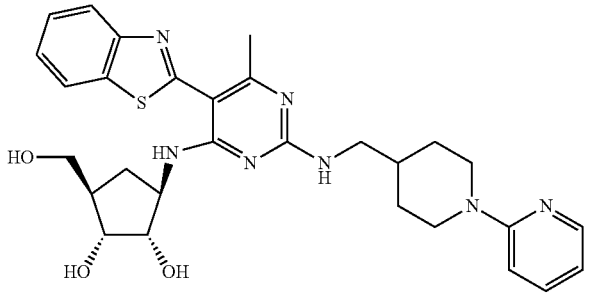
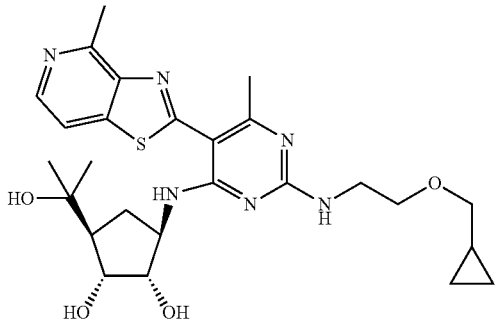
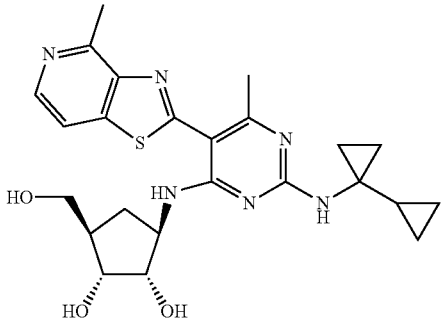
4415	
4410	
4416	
4417	

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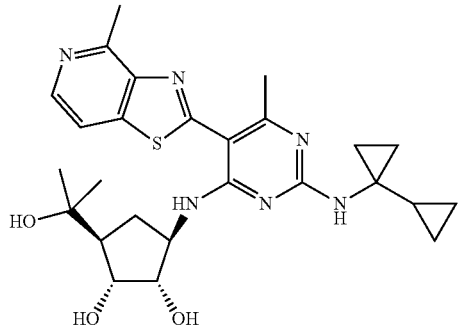
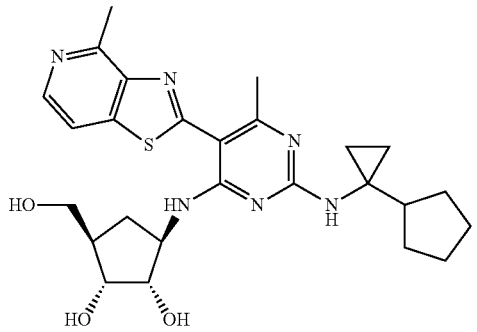
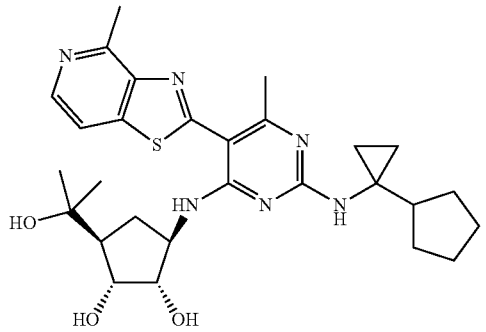
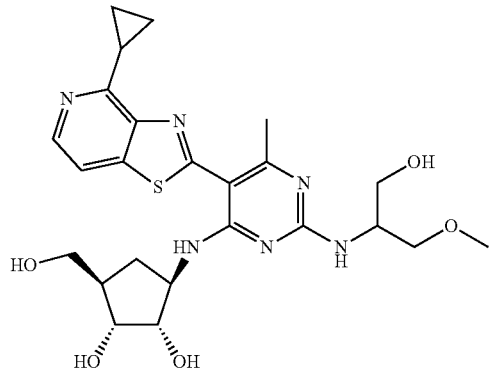
Compd #	Structure
4425	
4418	
4426	
4420	

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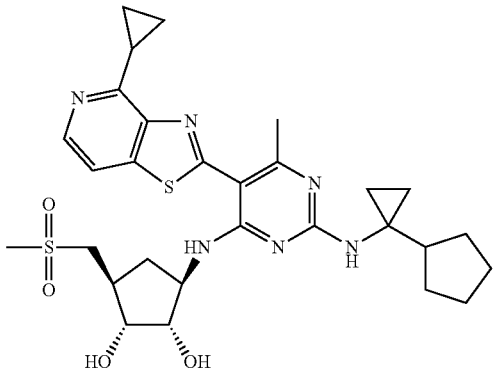
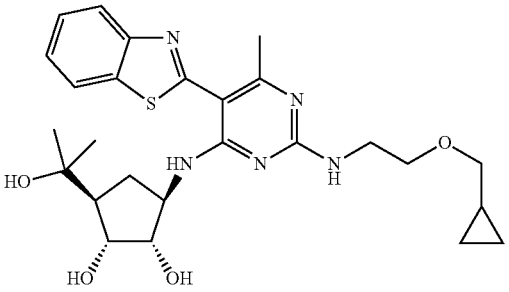
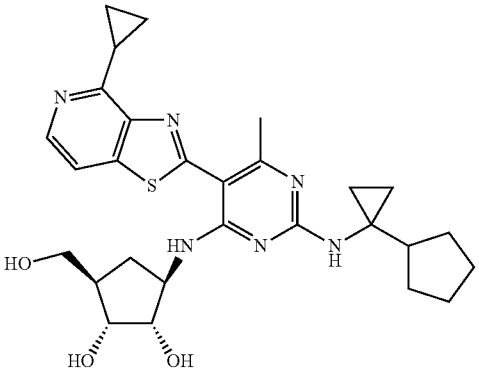
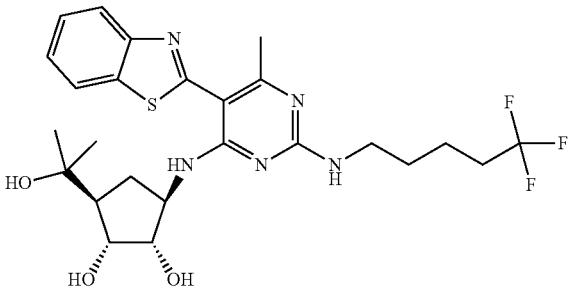
4427	
4421	
4428	
4422	

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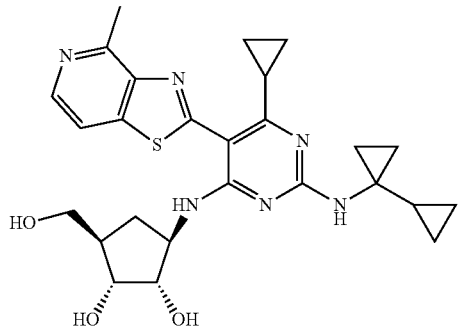
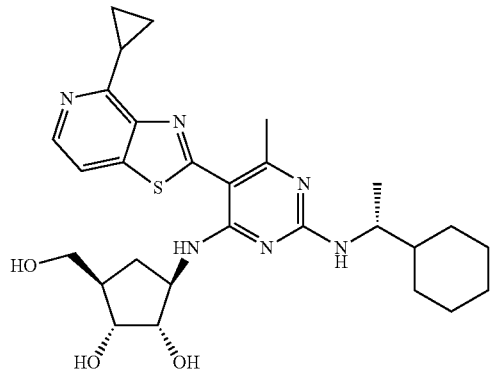
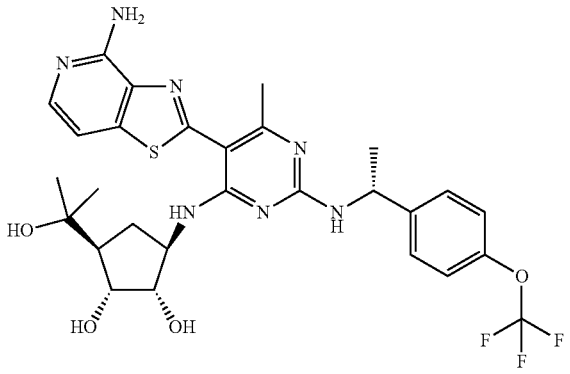
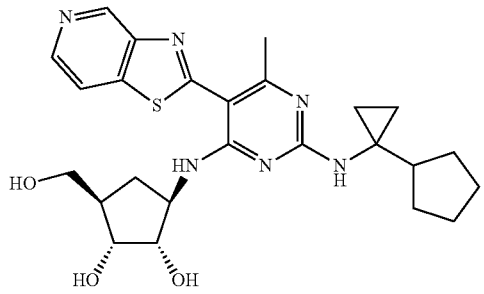
4429	
4424	
4431	
4432	

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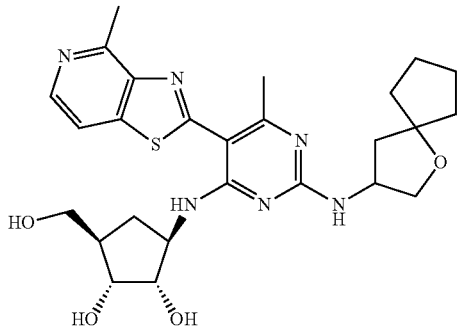
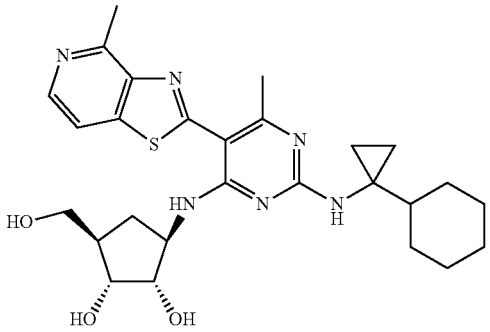
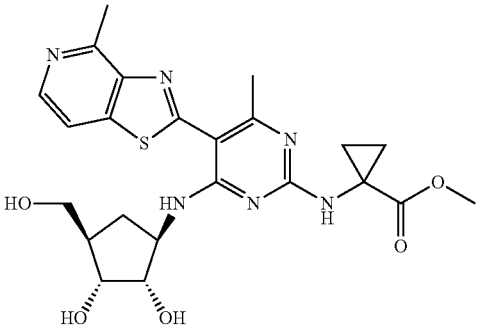
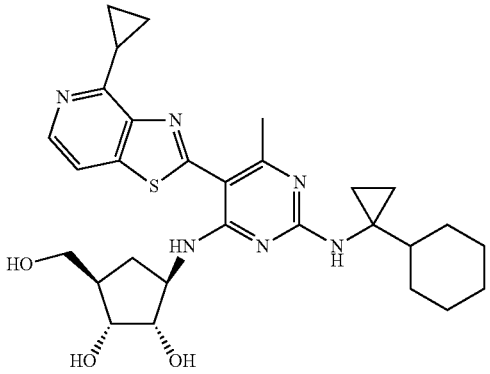
4438	
4433	
4439	
4434	

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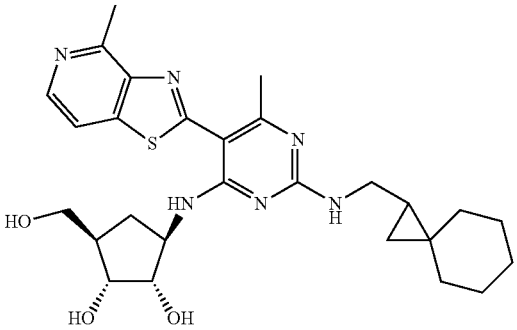
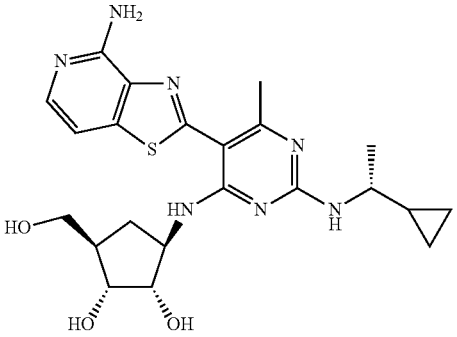
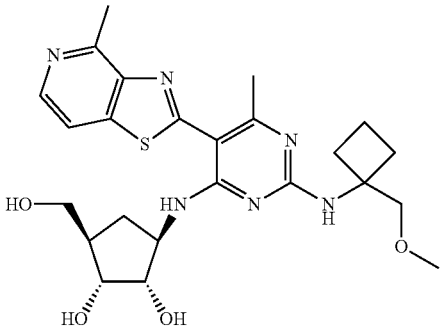
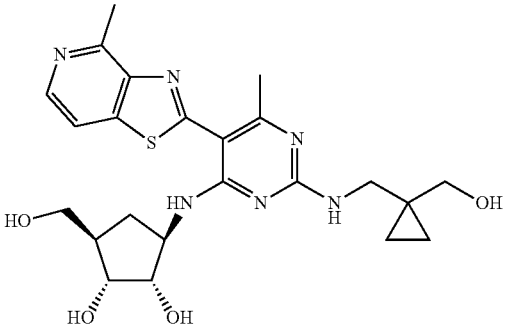
4440	
4435	
4441	
4436	

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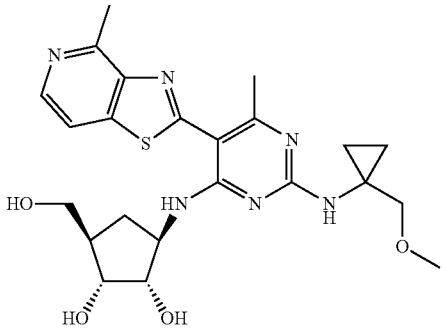
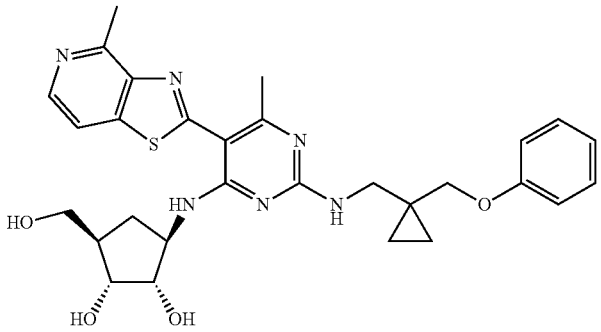
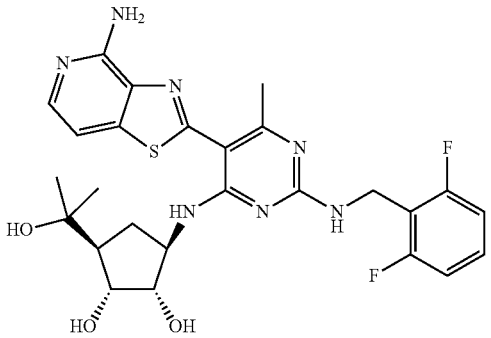
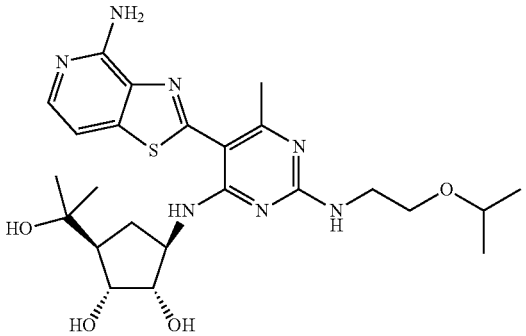
4442	
4437	
4443	
4444	

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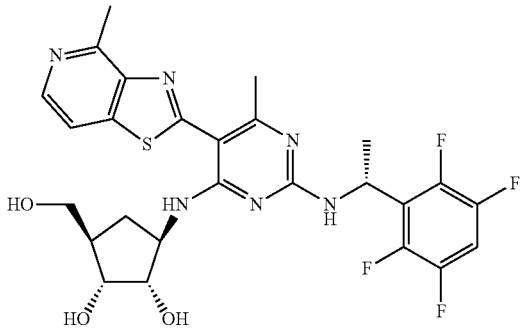
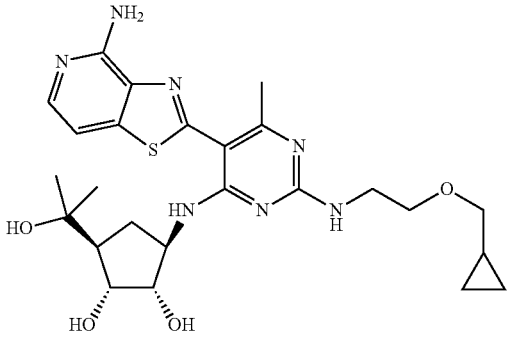
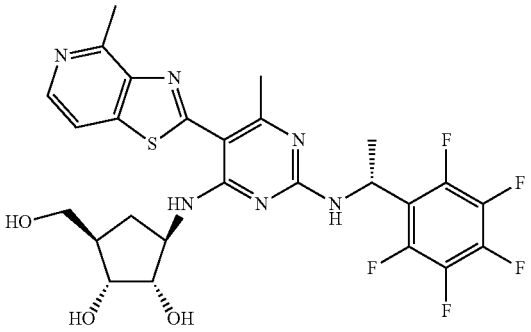
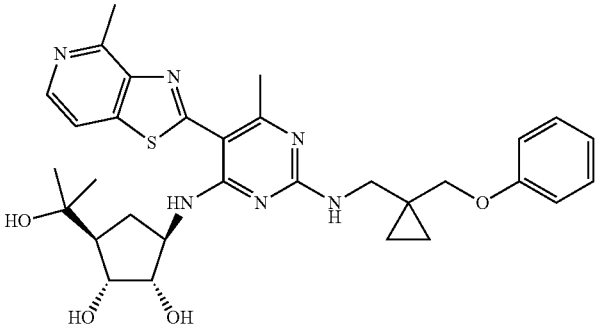
4449	
4445	
4450	
4446	

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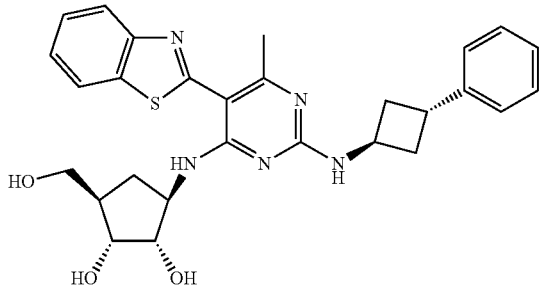
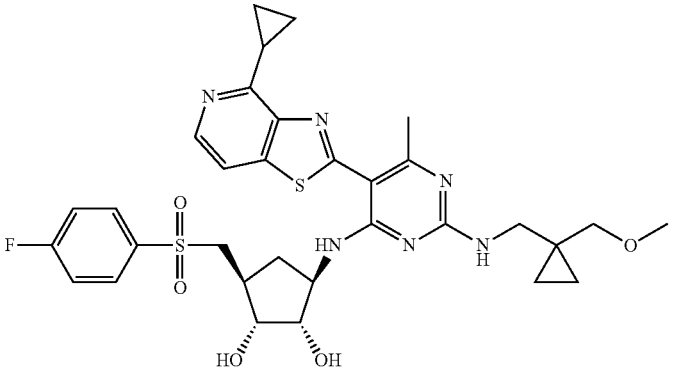
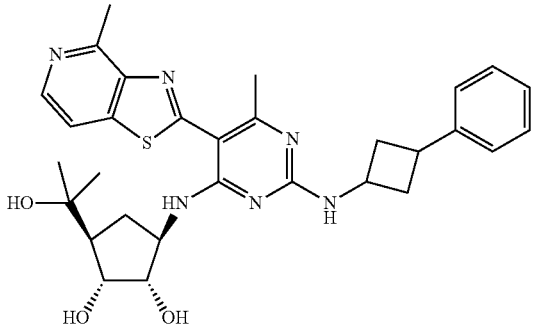
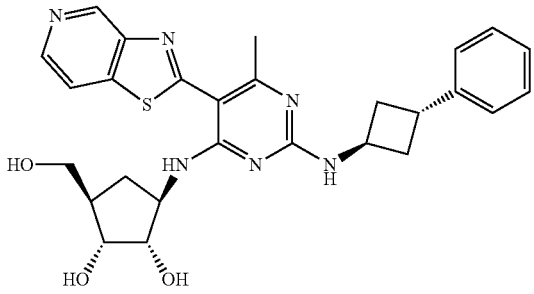
4503	
4448	
4511	
4505	

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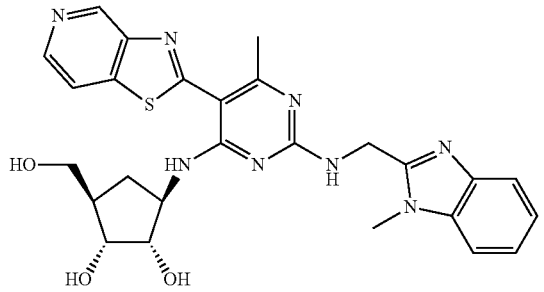
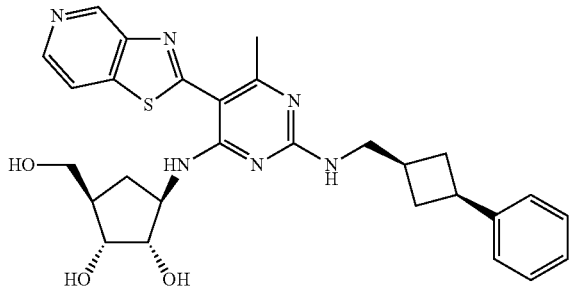
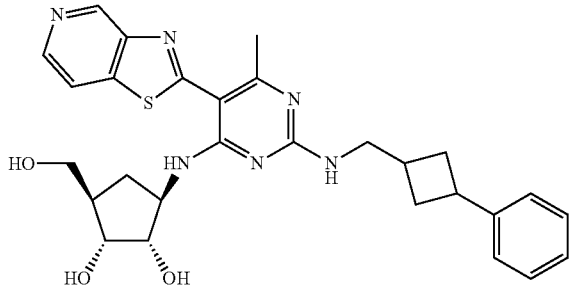
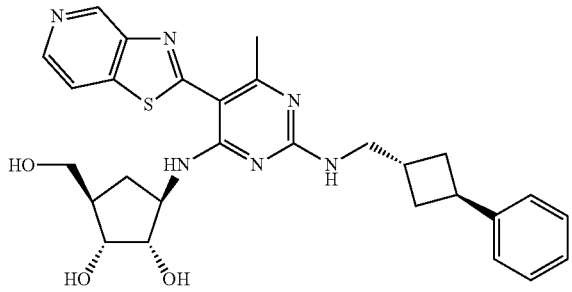
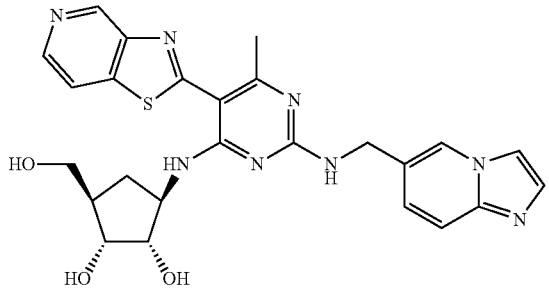
4506	
4512	
4507	
4513	
4508	

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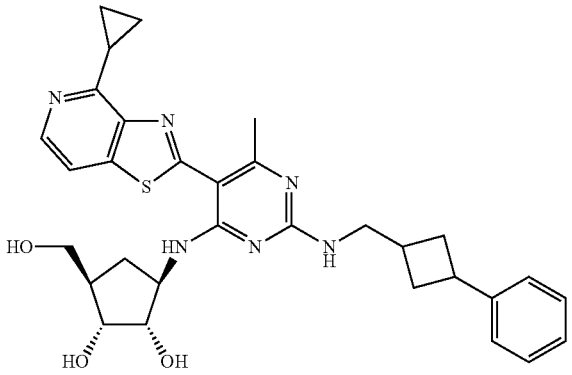
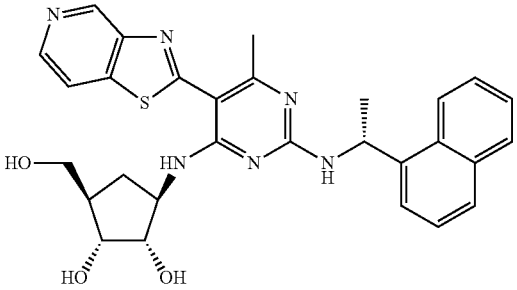
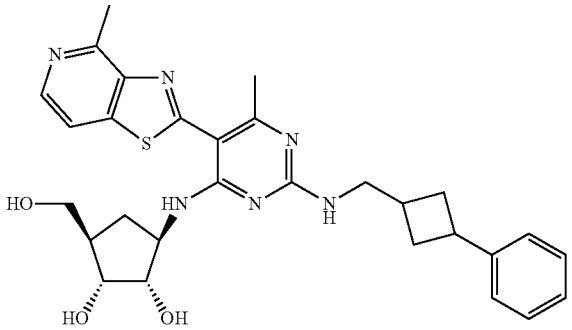
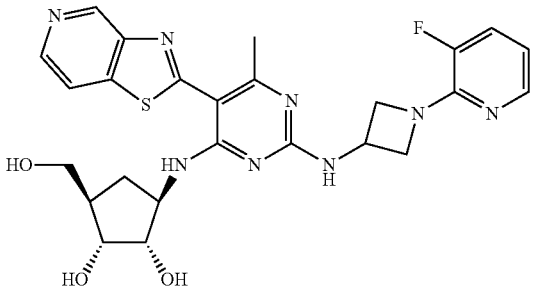
4515	
4509	
4516	
4510	

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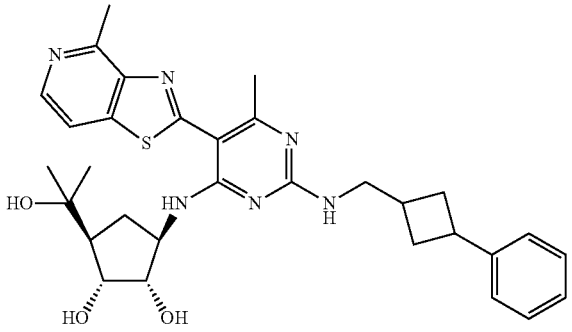
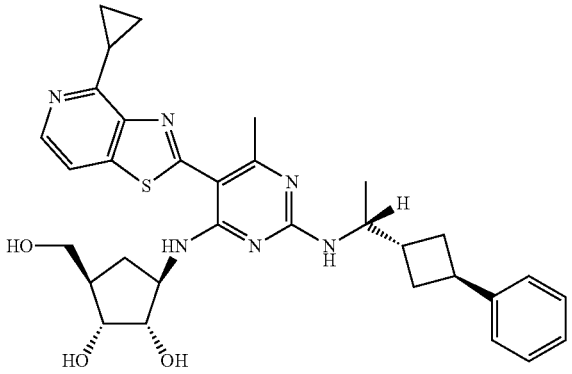
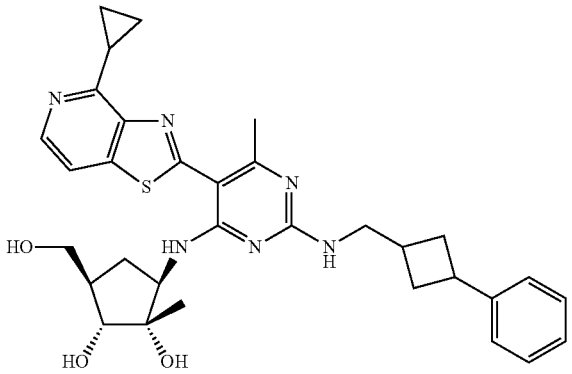
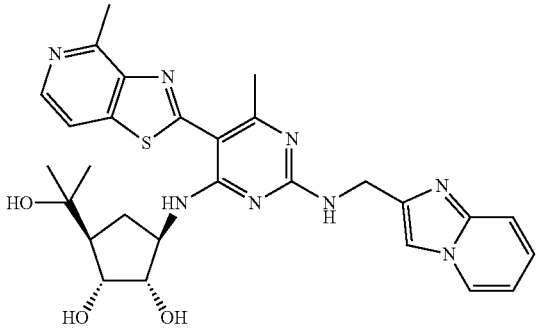
4517	
4518	
4524	
4520	

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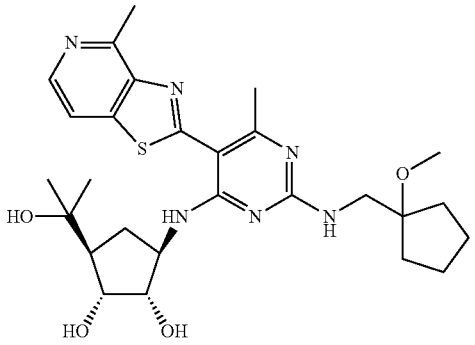
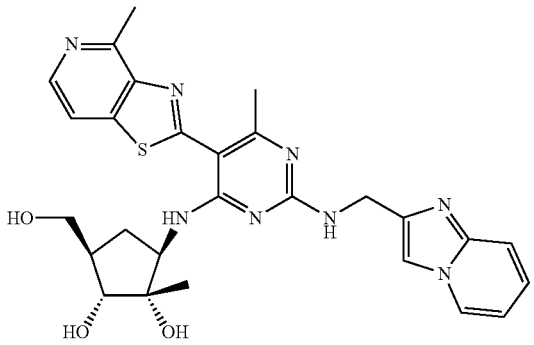
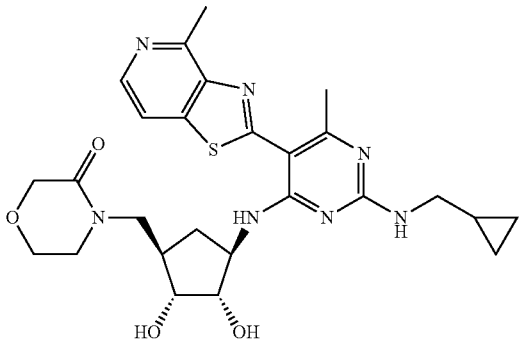
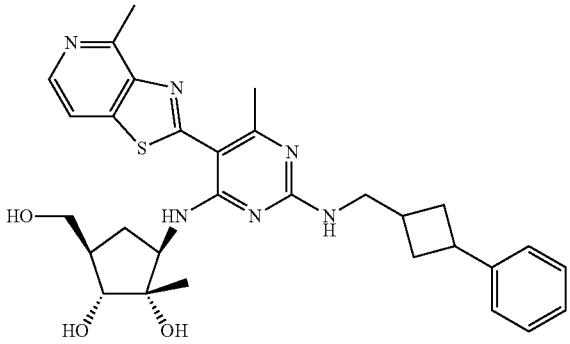
4527	
4521	
4530	
4522	

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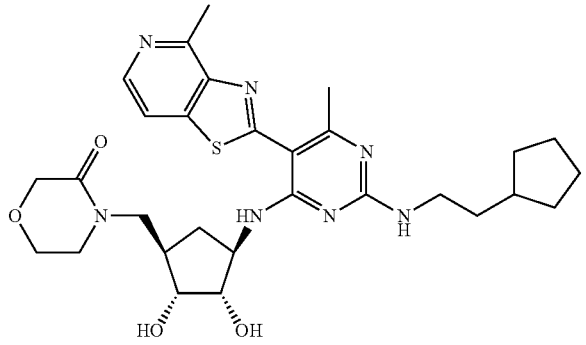
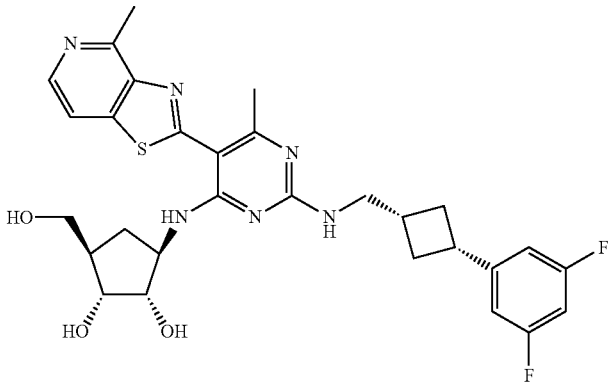
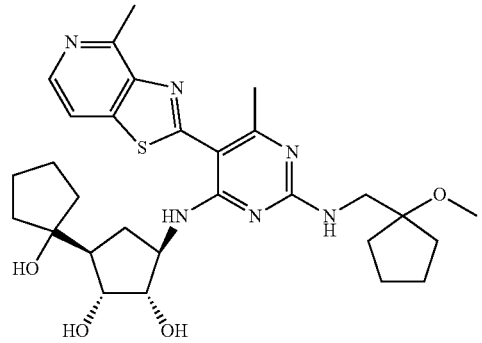
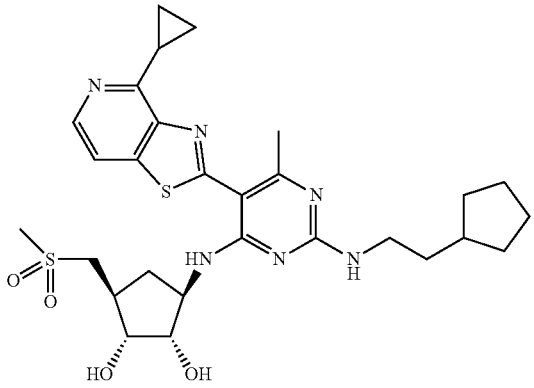
4531	
4523	
4538	
4533	

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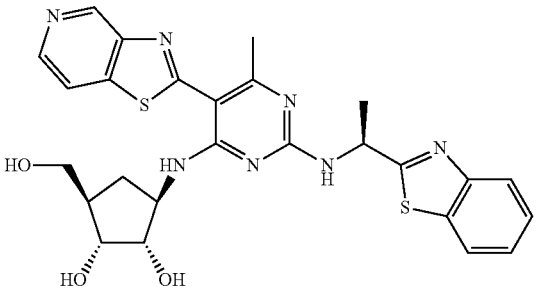
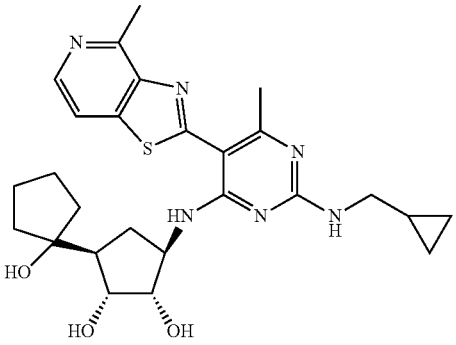
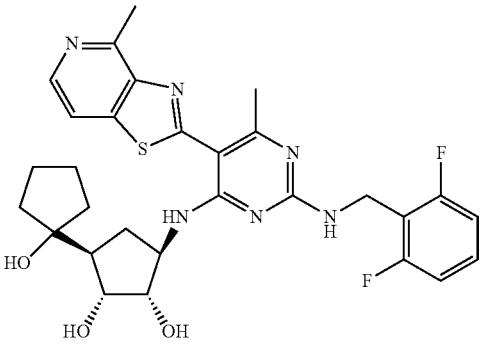
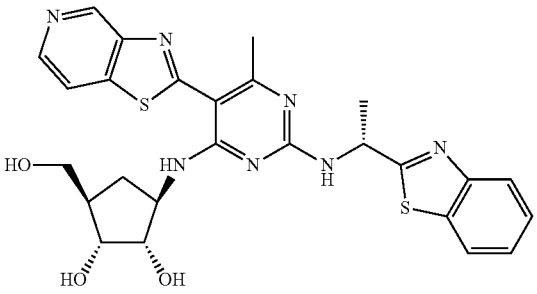
4601	
4534	
4535	
4602	

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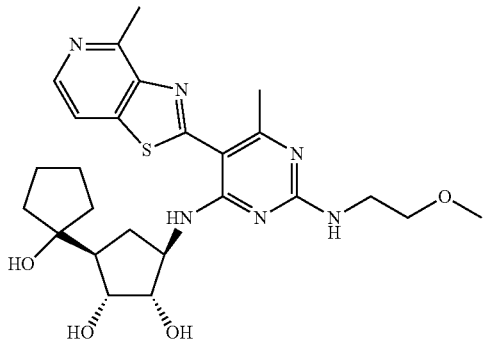
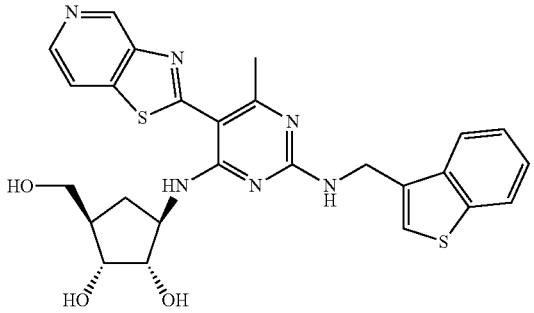
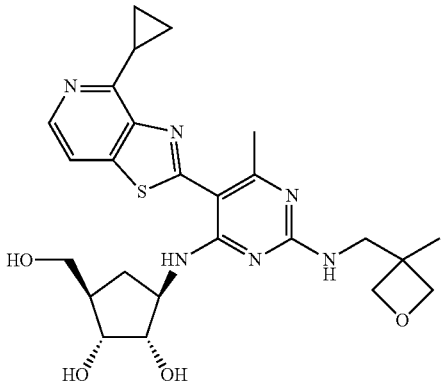
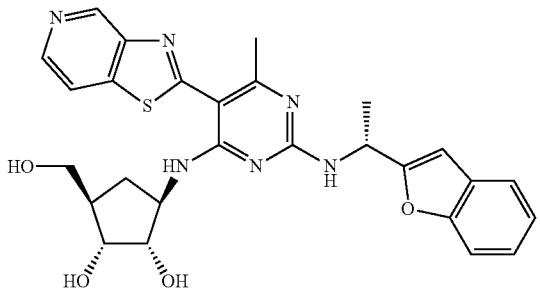
4536	
4603	
4537	
4607	

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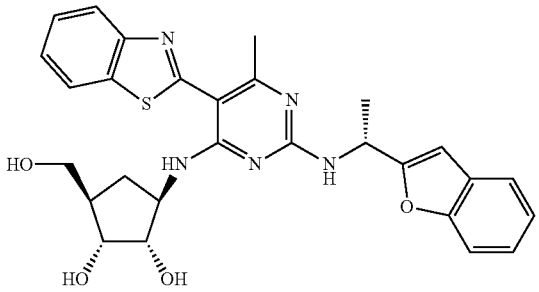
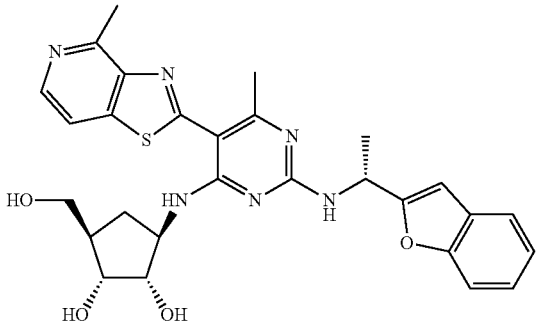
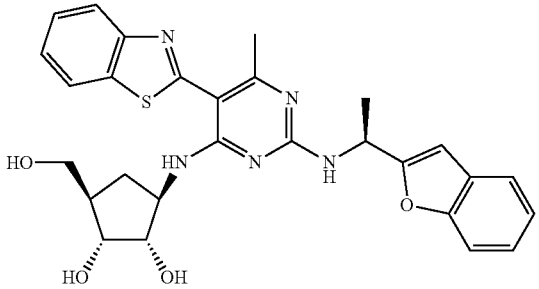
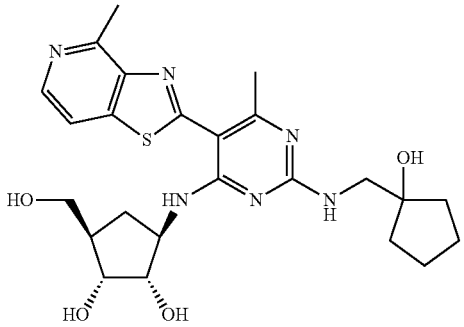
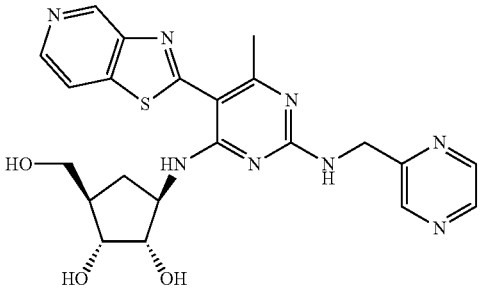
4608	
4619	
4611	
4621	
4614	

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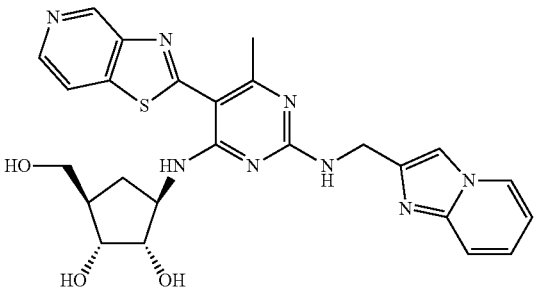
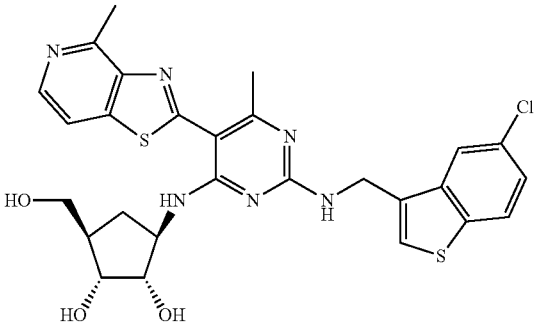
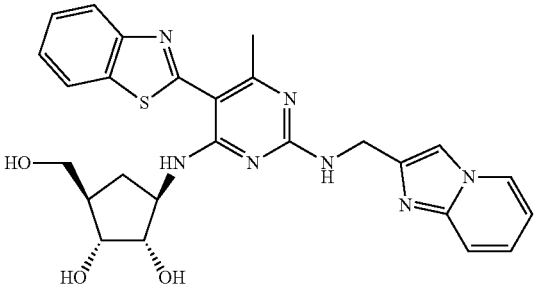
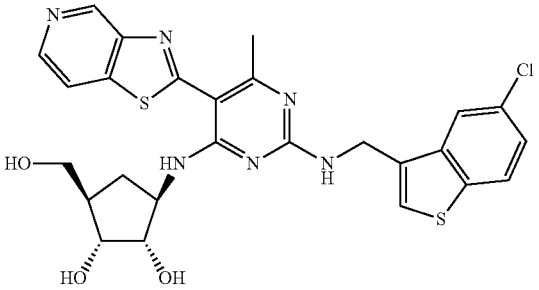
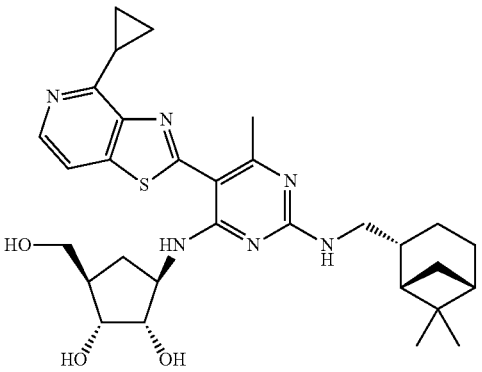
4623	
4615	
4624	
4616	
4625	

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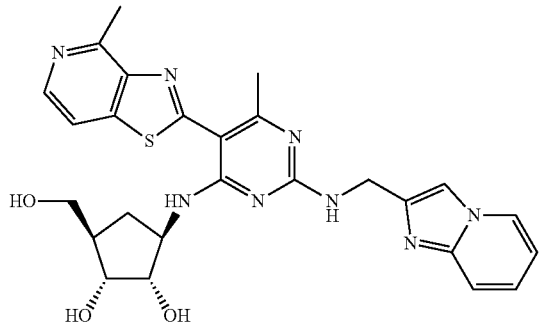
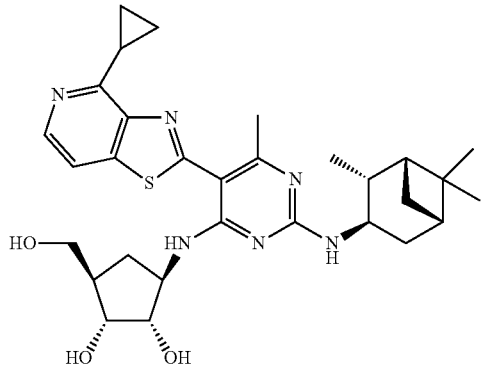
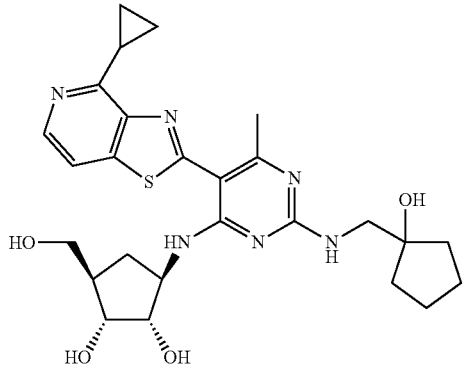
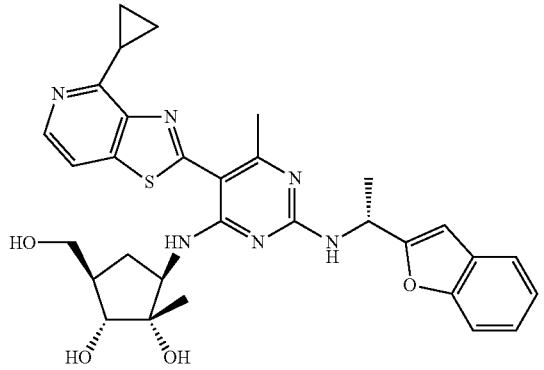
4618	
4626	
4627	
4633	

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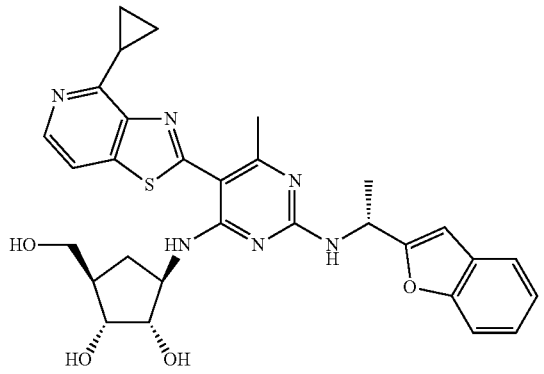
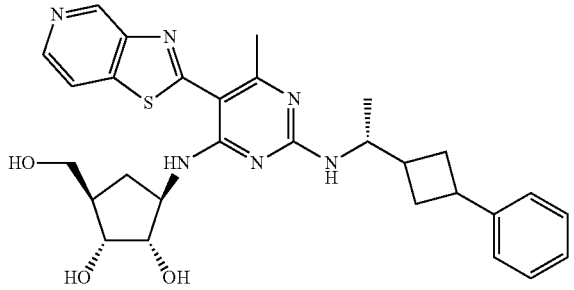
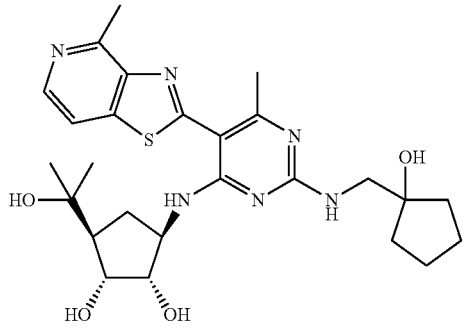
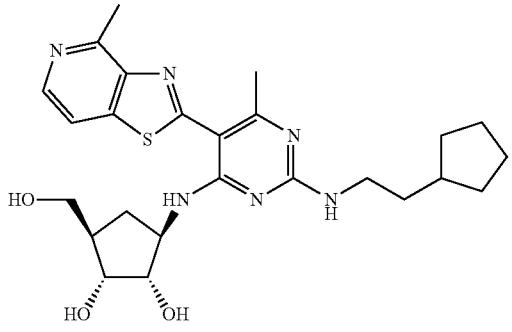
4628	
4634	
4629	
4635	

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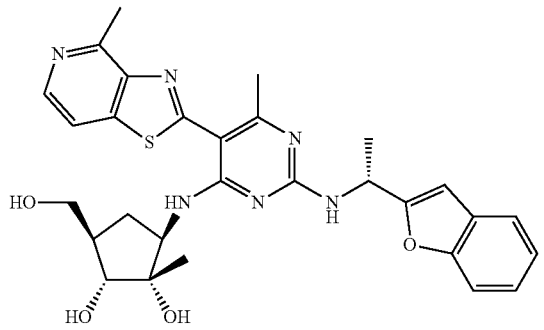
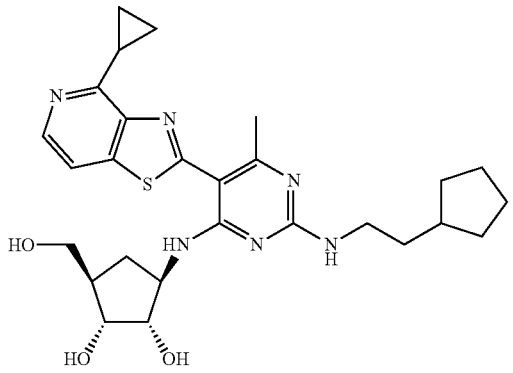
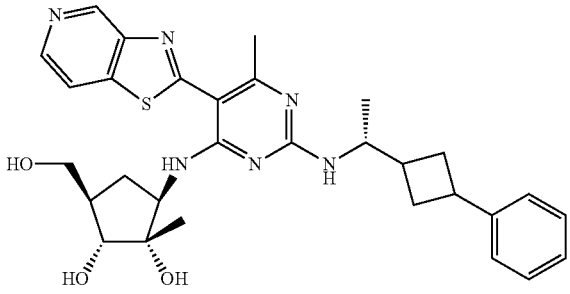
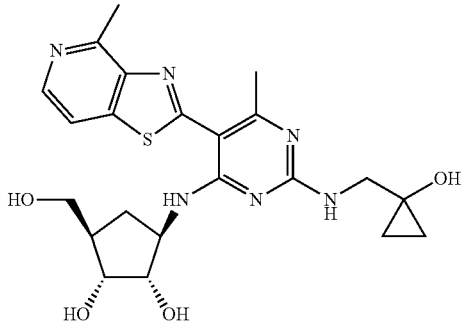
4631	
4636	
4632	
4637	

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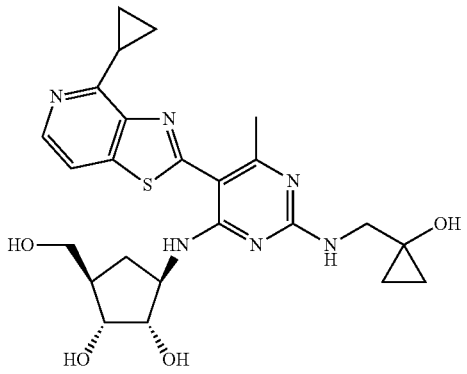
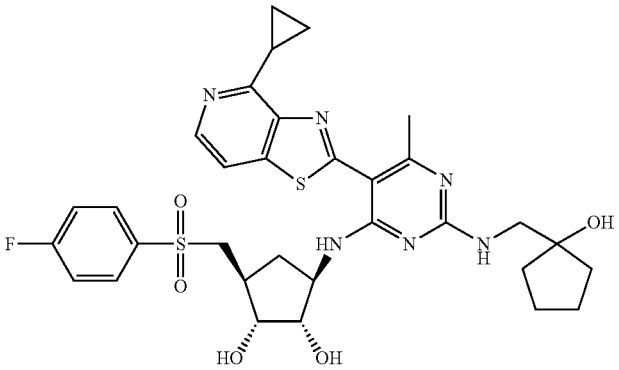
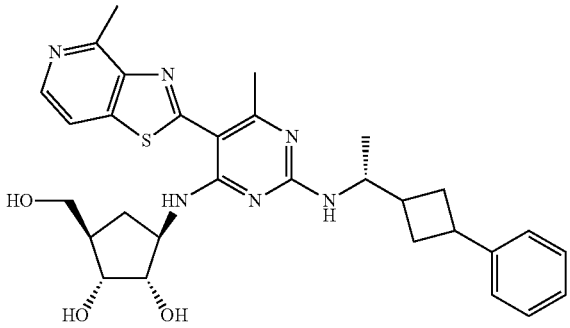
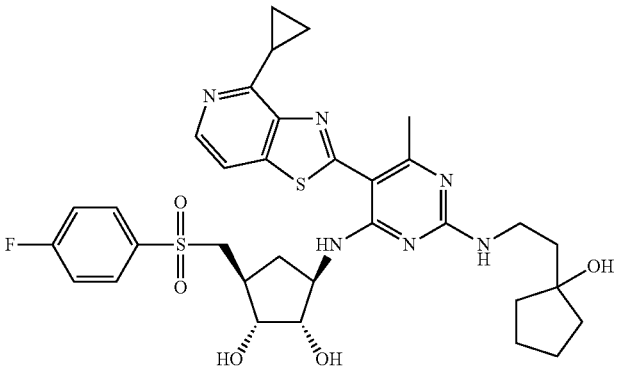
4638	
4643	
4639	
4644	

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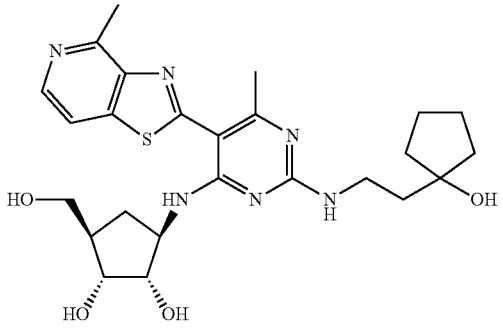
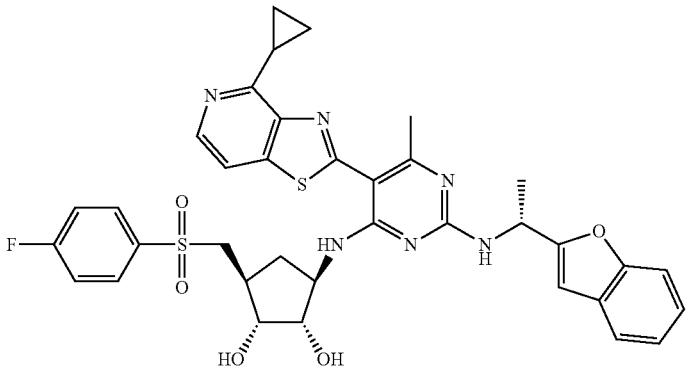
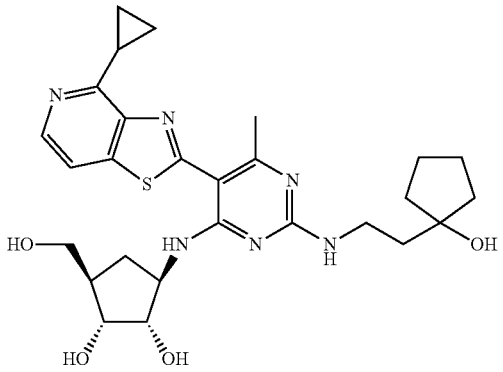
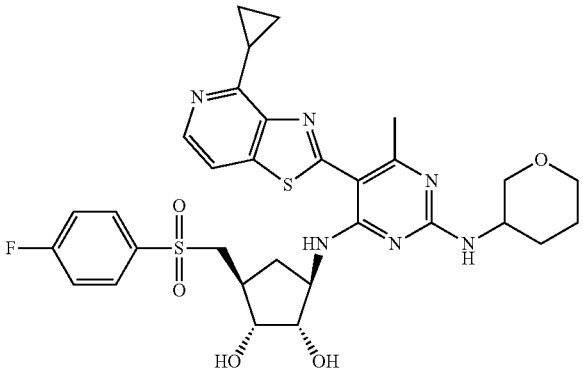
4640	
4645	
4641	
4646	

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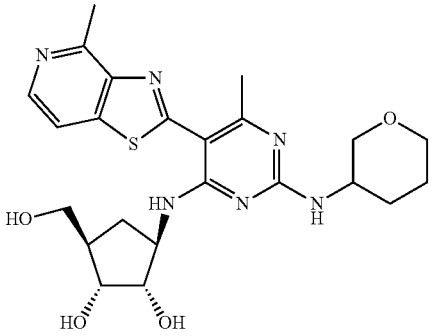
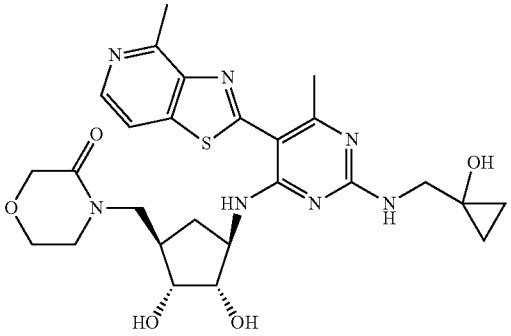
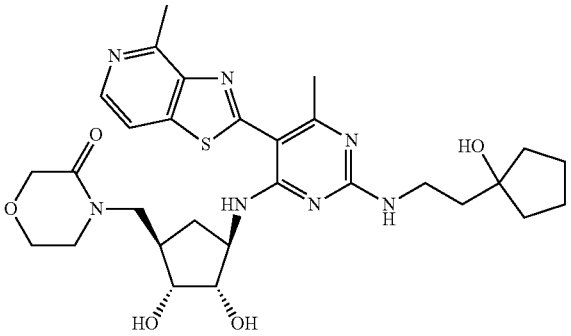
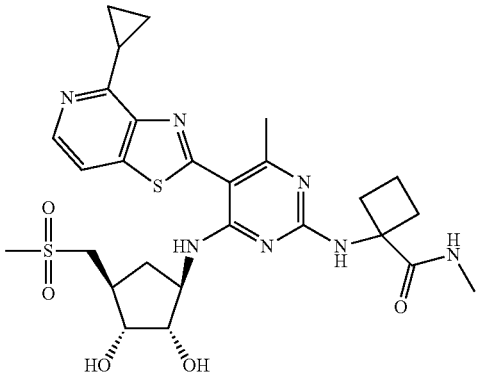
4642	
4647	
4648	
4654	

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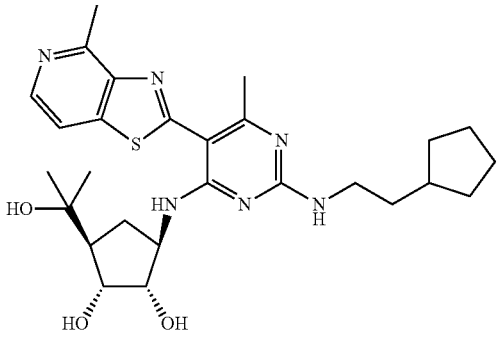
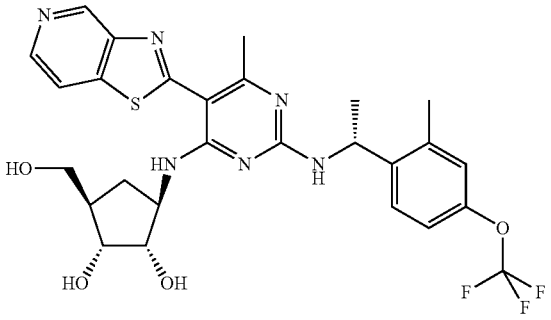
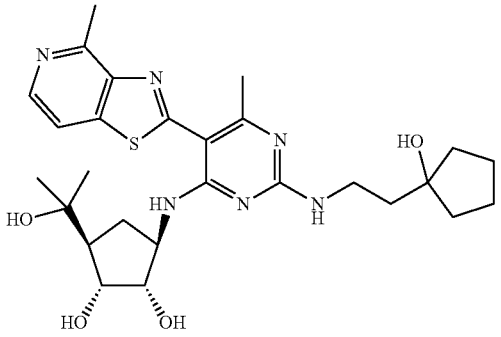
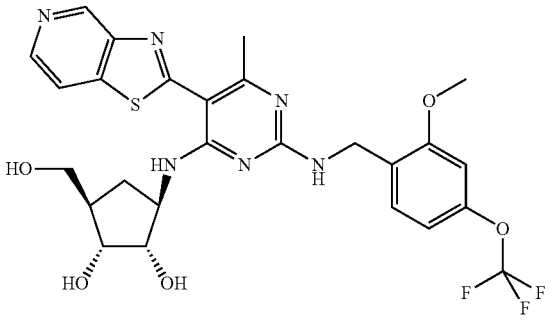
4649	
4701	
4650	
4702	

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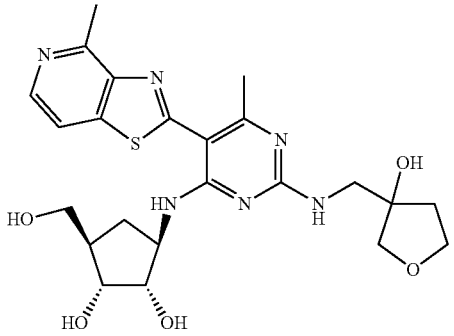
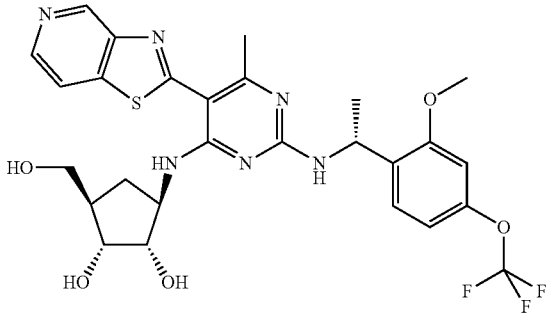
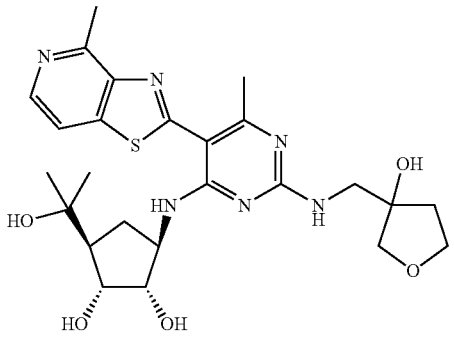
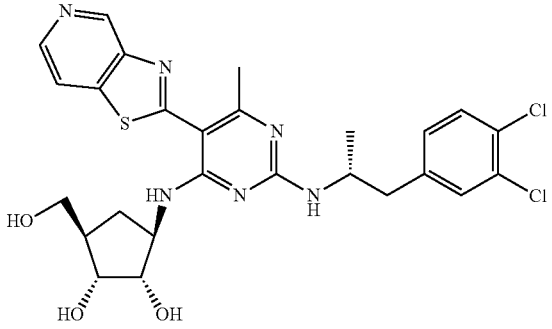
4651	
4703	
4652	
4704	

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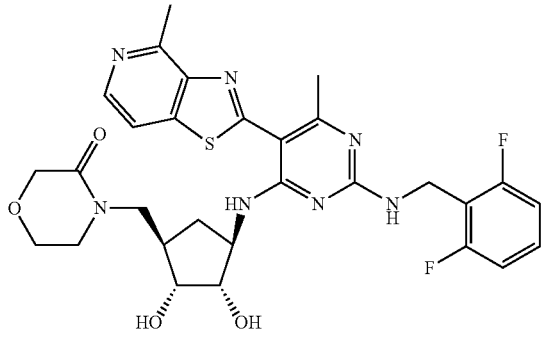
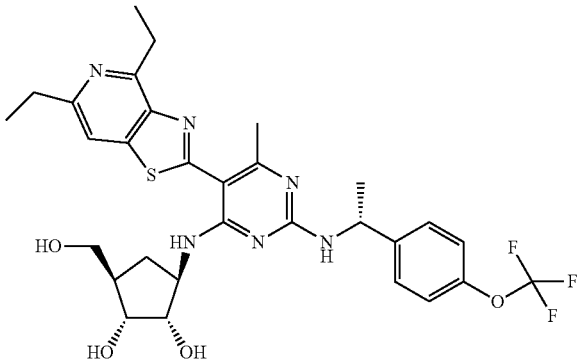
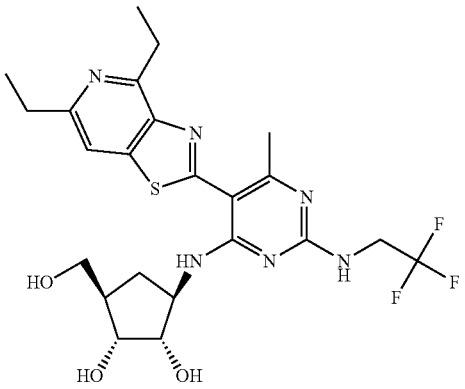
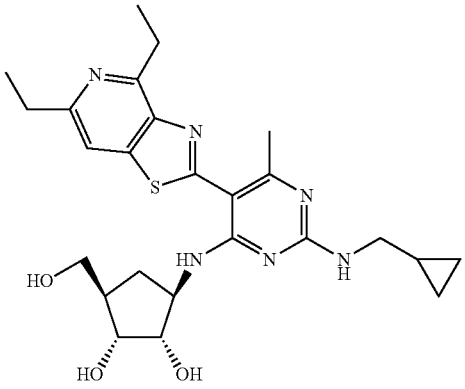
4653	
4705	
4706	
4713	

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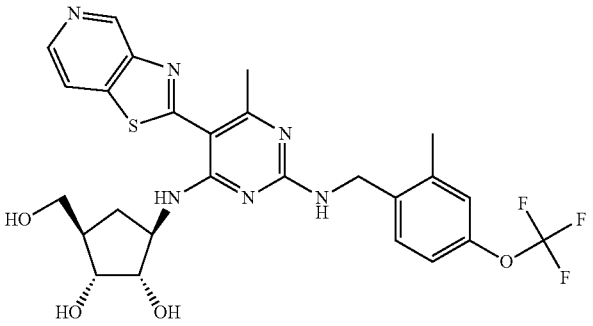
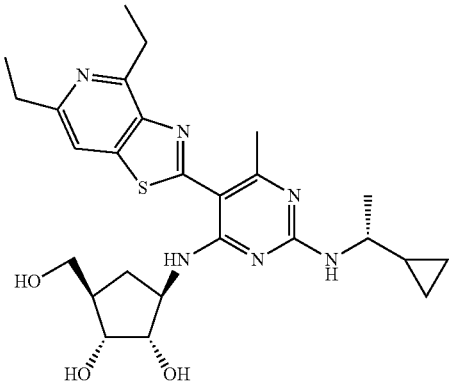
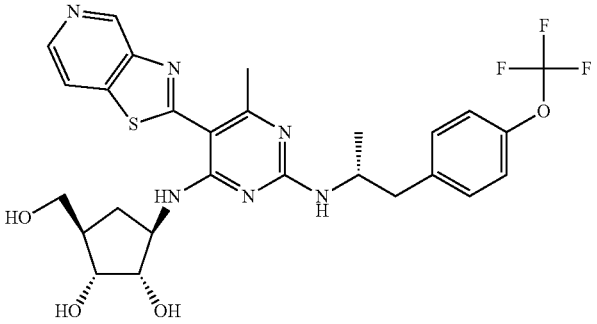
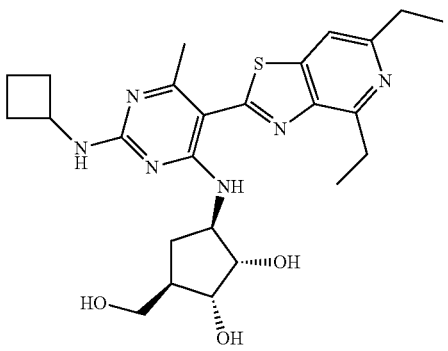
4707	
4714	
4708	
4715	

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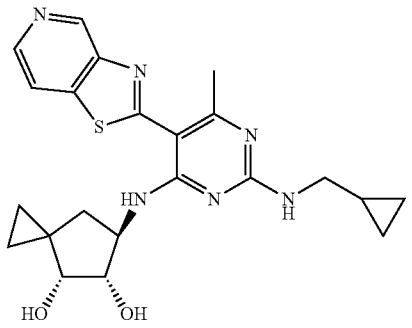
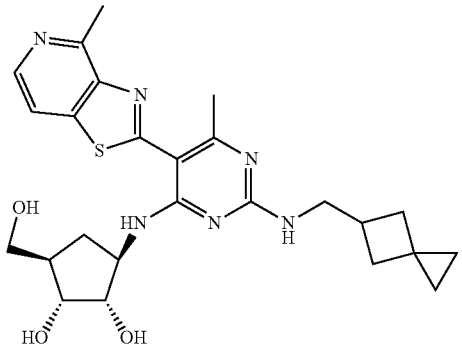
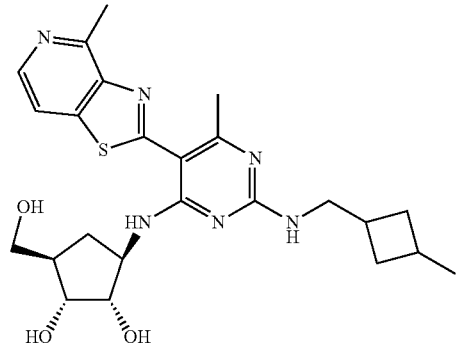
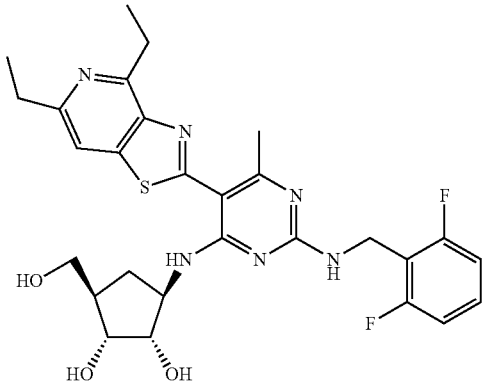
4711	
4716	
4712	
4717	

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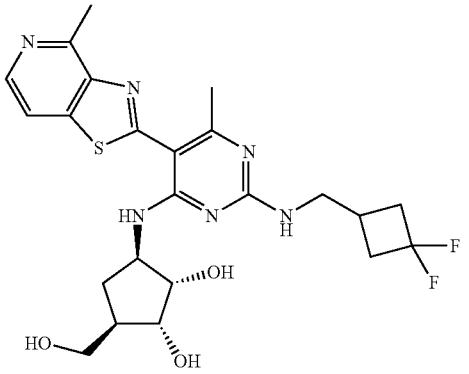
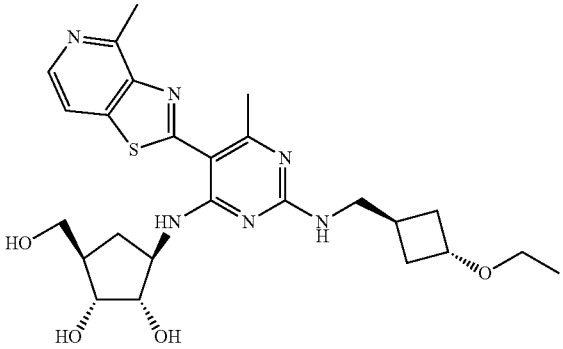
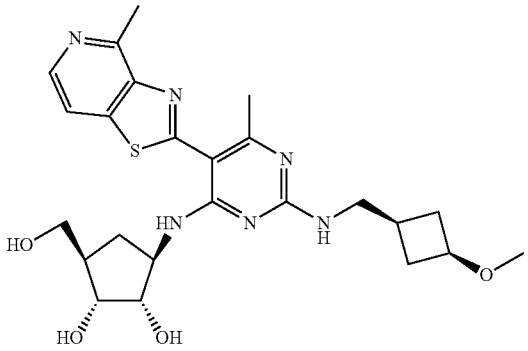
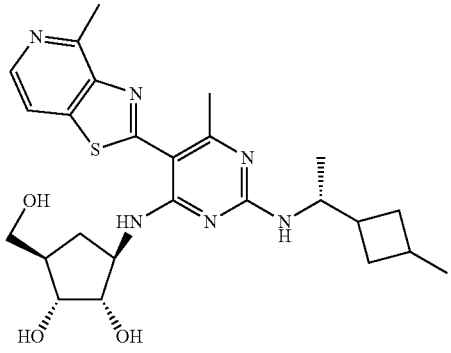
4718	
4724	
4719	
4726	

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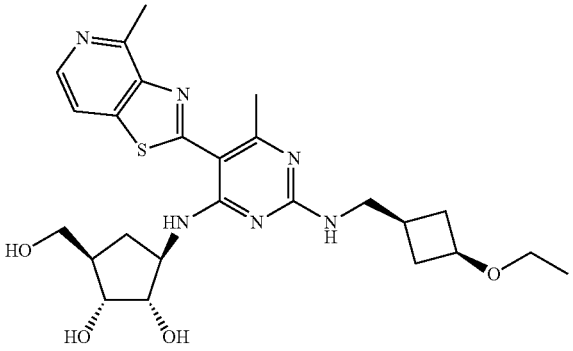
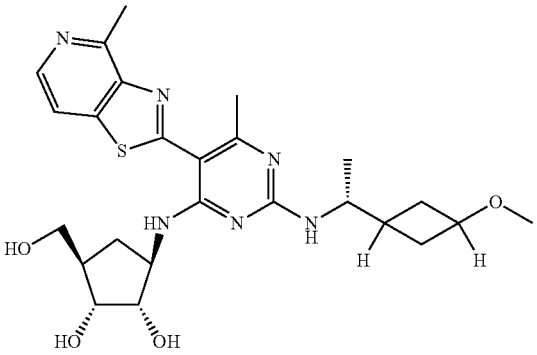
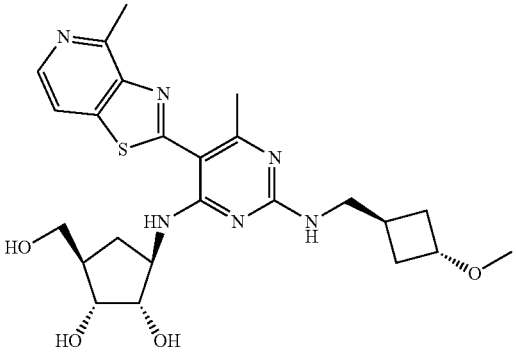
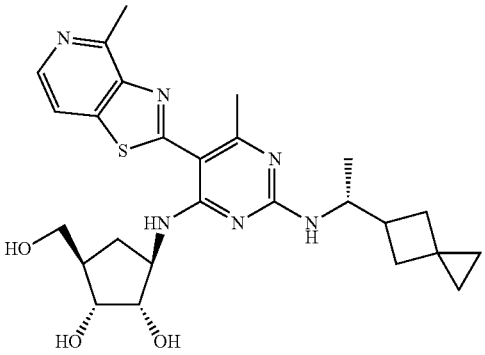
4721	
4727	
4722	
4723	

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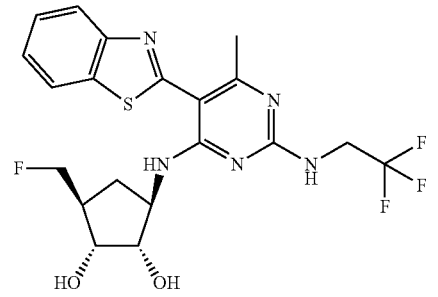
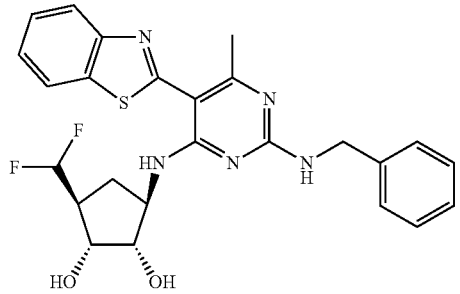
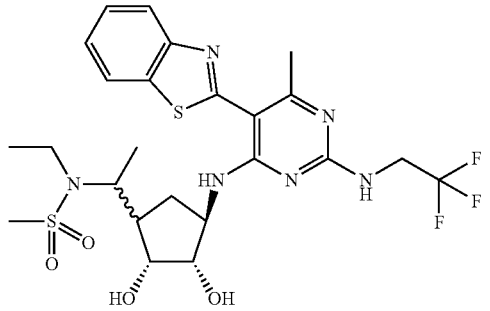
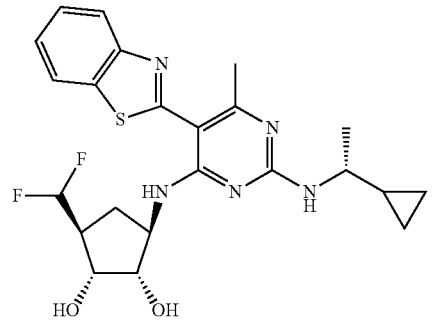
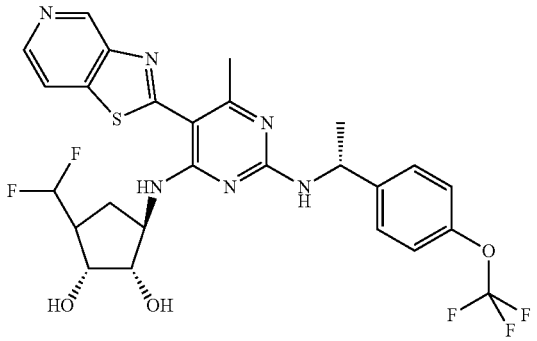
3000	
3012	
3003	
3014	
3004	

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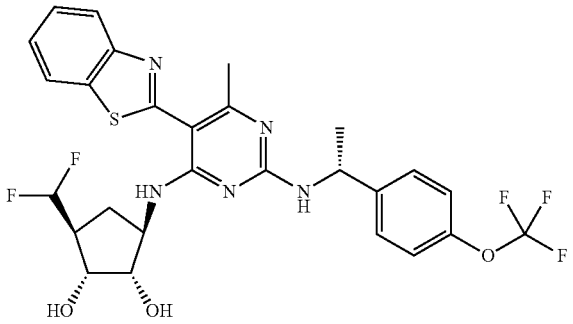
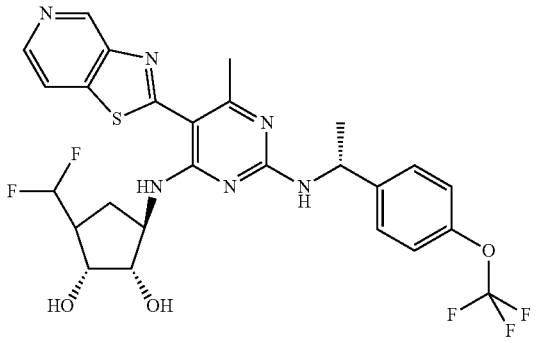
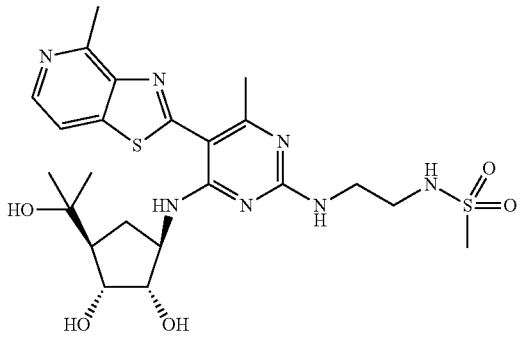
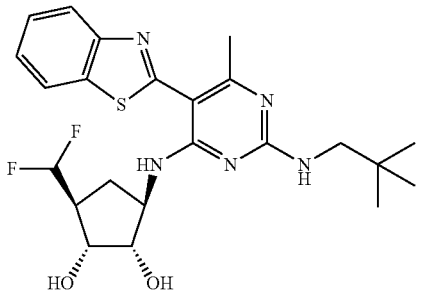
3015	
3005	
3027	
3008	

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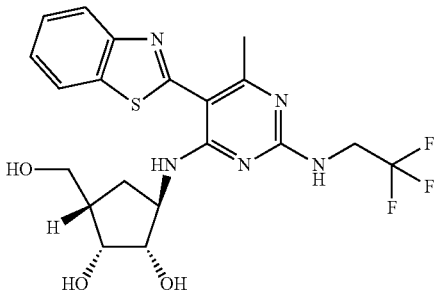
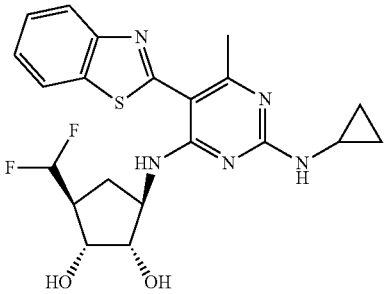
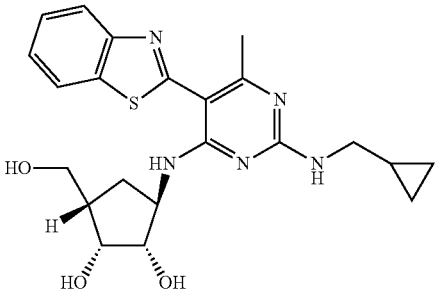
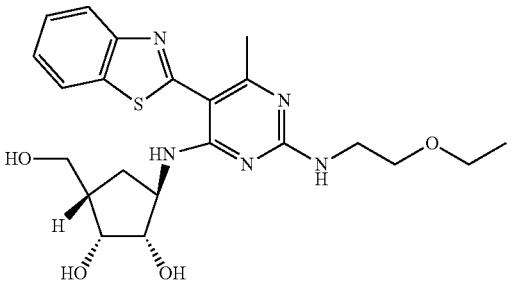
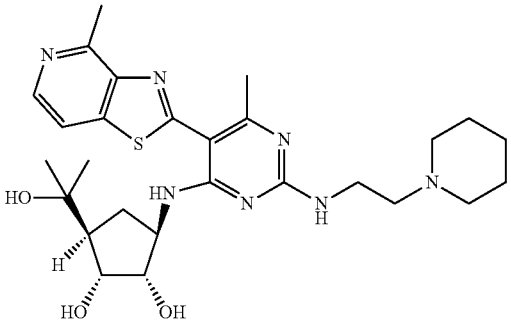
3101	
3010	
3102	
3103	
3152	

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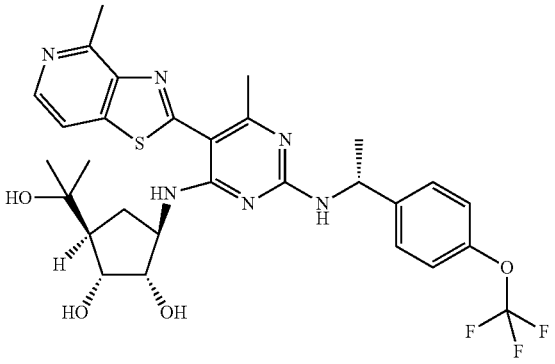
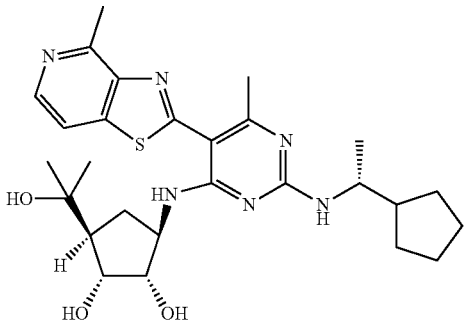
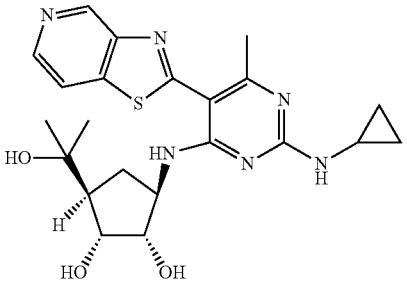
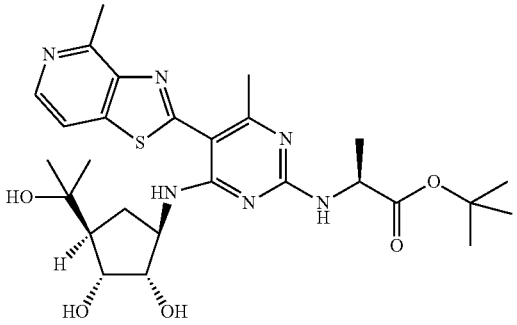
3110	
3173	
3128	
3180	

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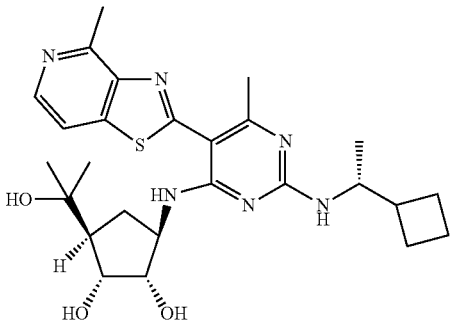
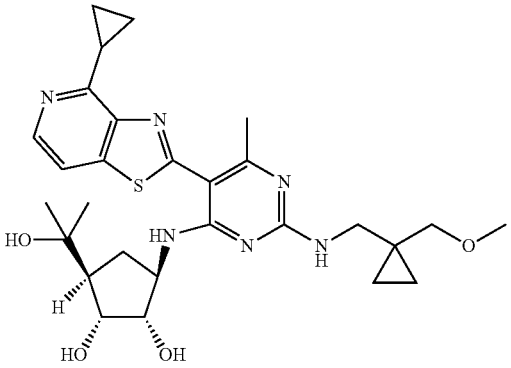
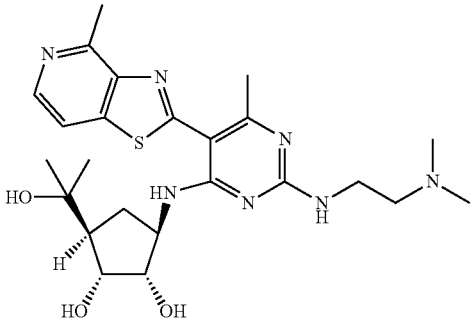
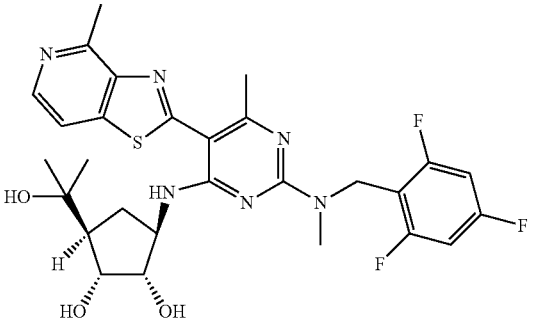
3140	
3203	
3143	
3223	

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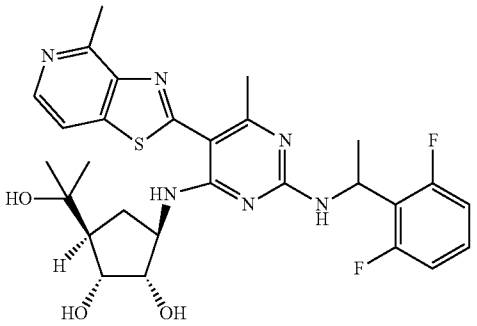
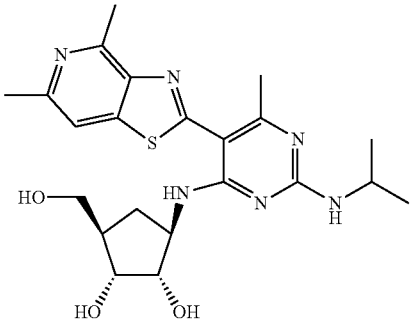
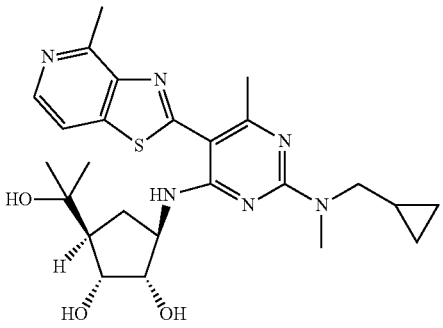
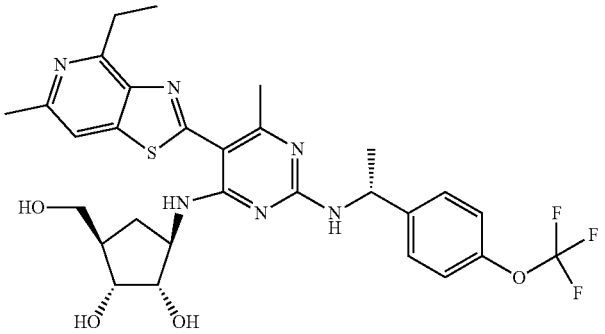
3151	
3407	
3235	
3410	

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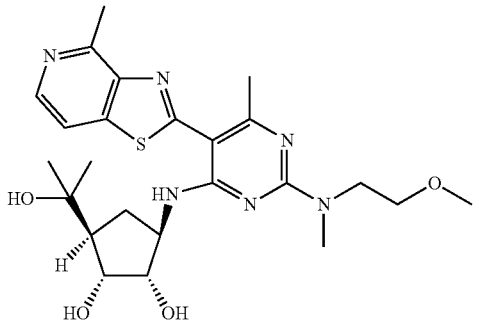
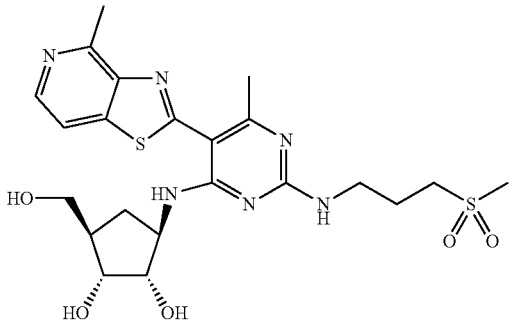
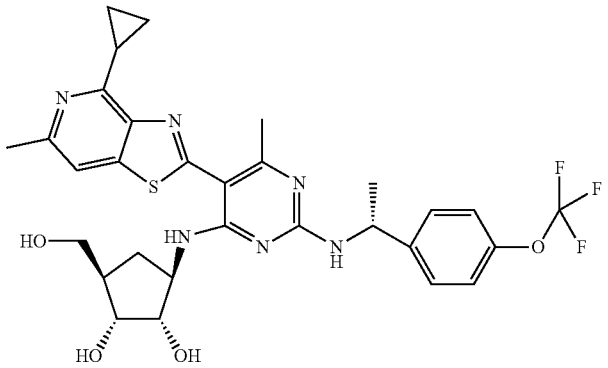
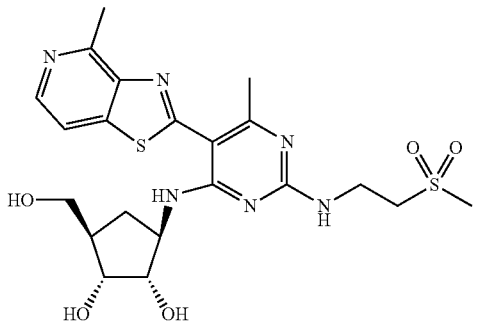
3236	
3311	
3413	
3312	

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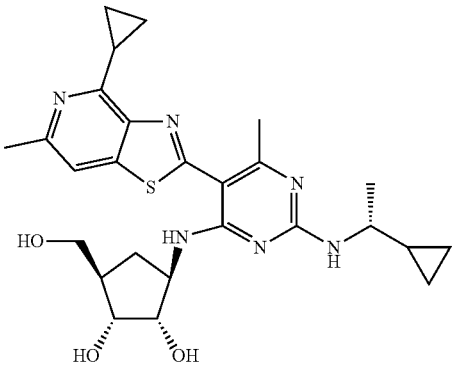
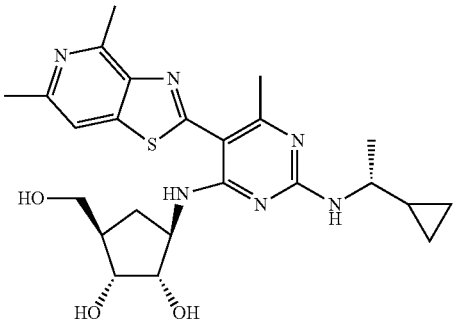
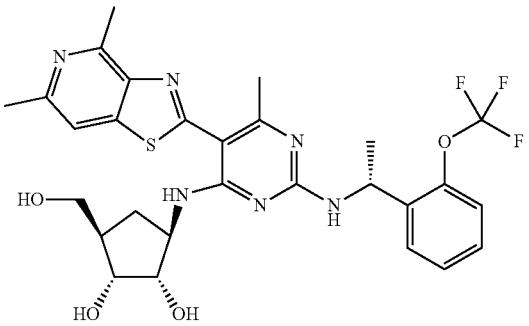
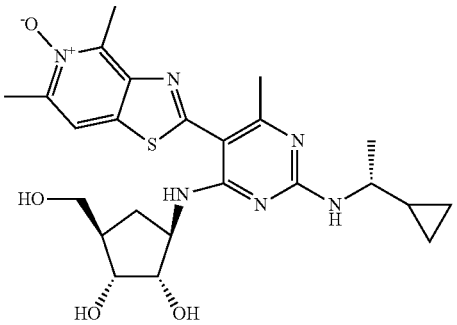
3414	
3403	
3420	
3404	

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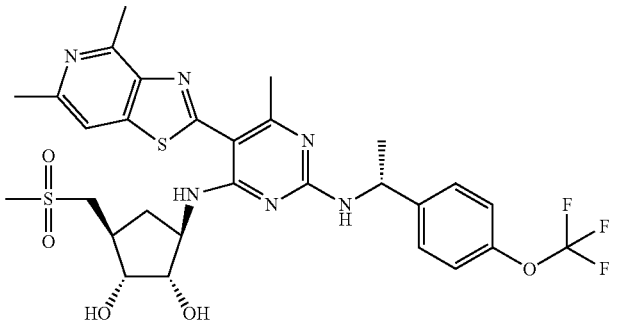
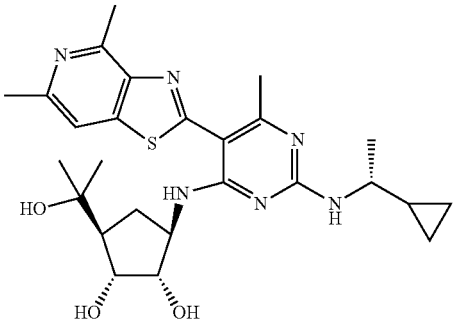
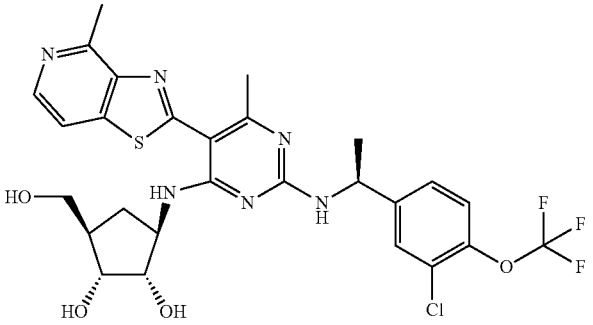
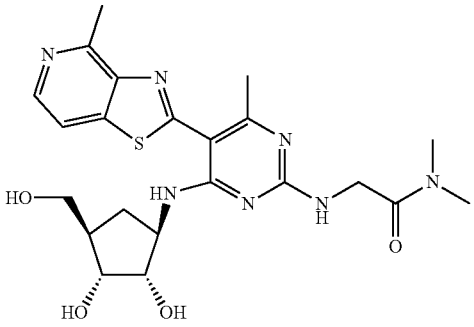
3422	
3423	
3710	
3452	

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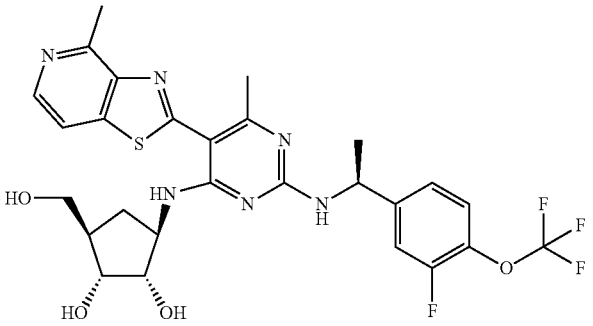
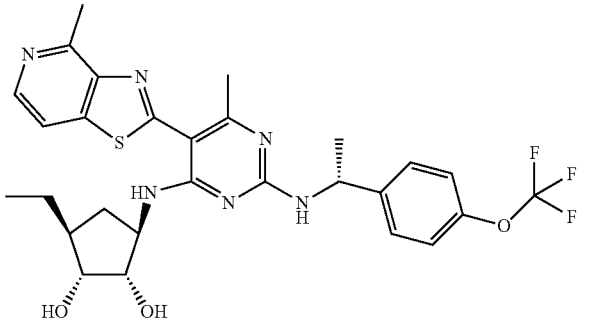
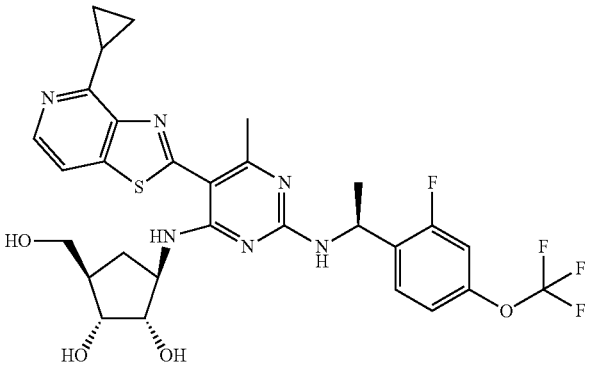
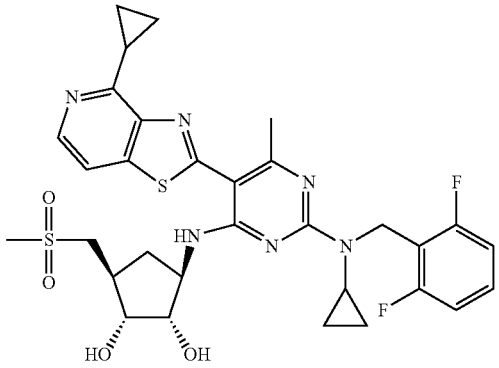
3713	
3559	
3839	
3595	

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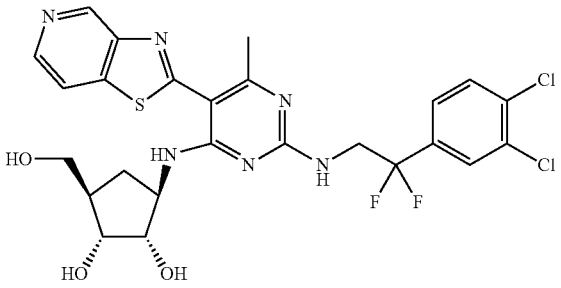
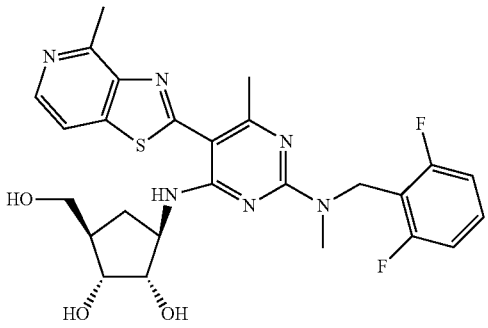
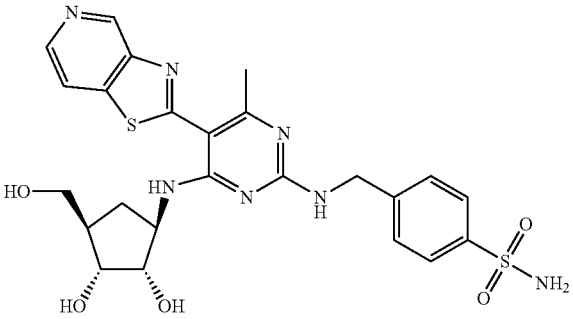
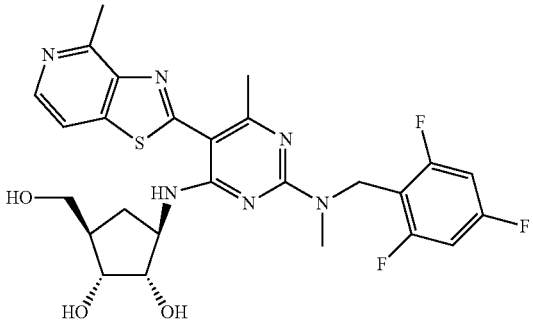
3902	
3596	
4005	
3597	

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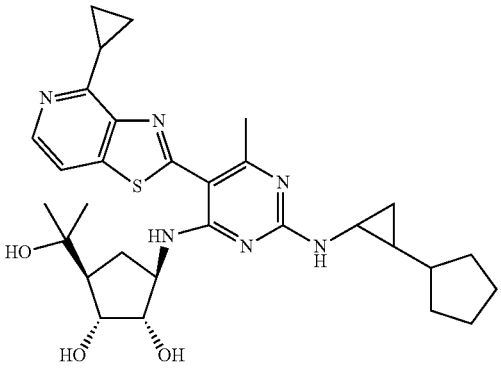
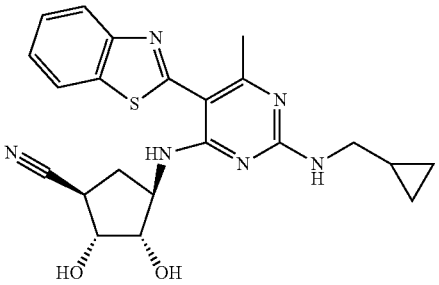
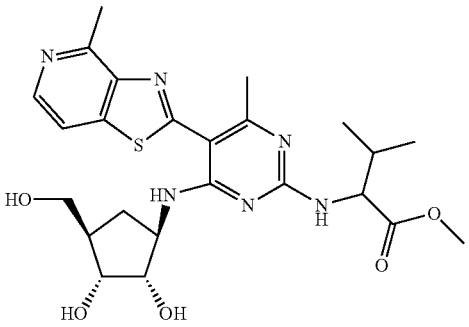
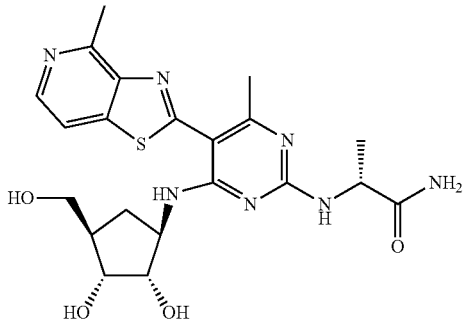
4216	
4113	
4218	
4118	

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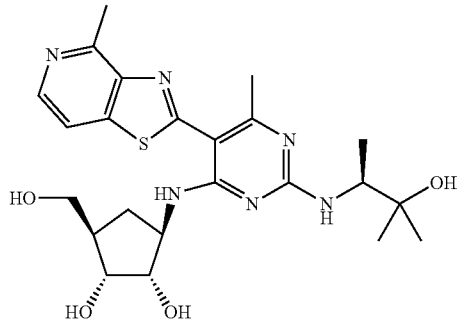
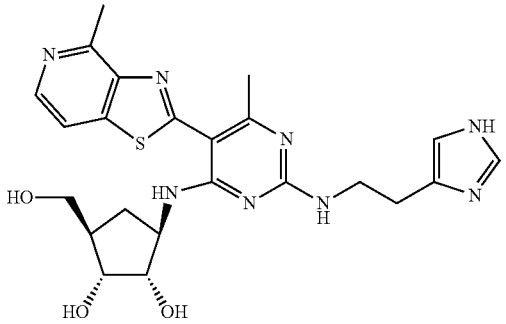
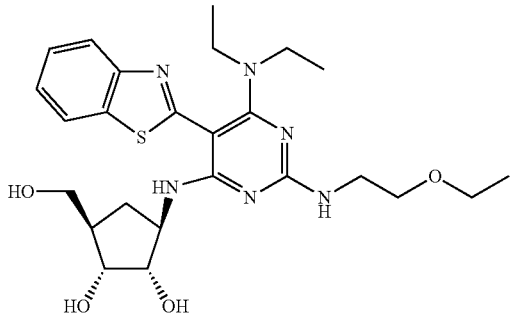
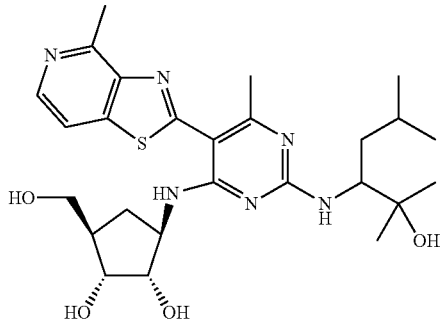
4124	
4219	
4201	
4222	

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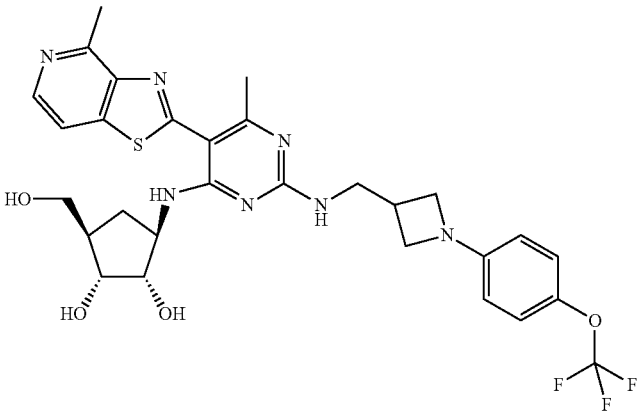
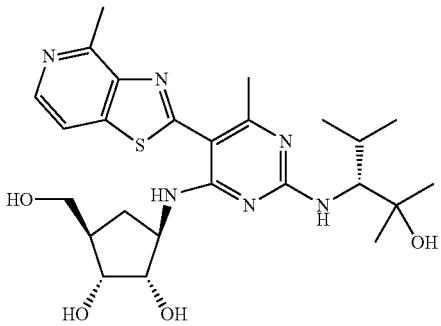
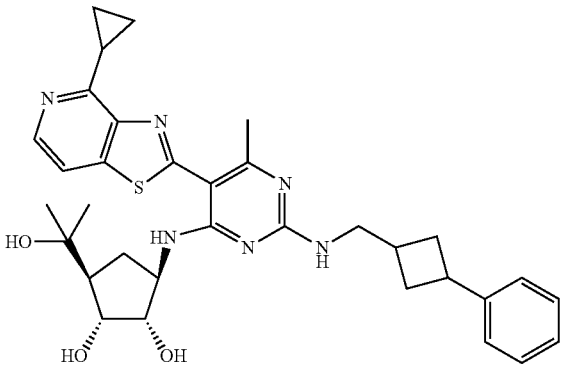
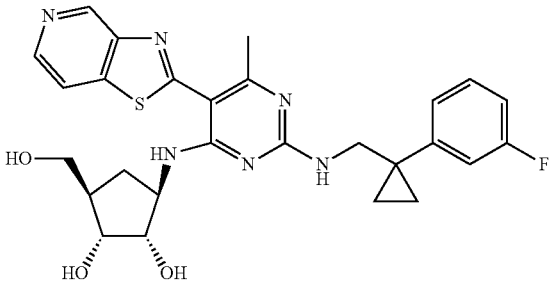
4209	
4224	
4214	
4315	

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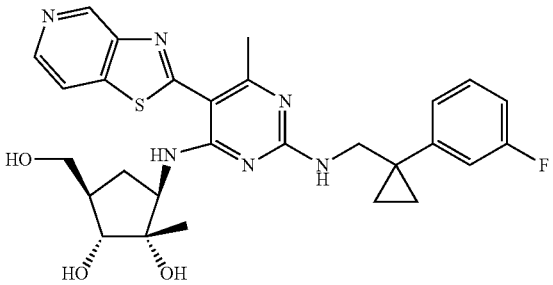
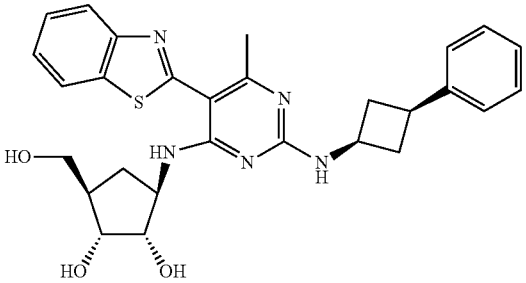
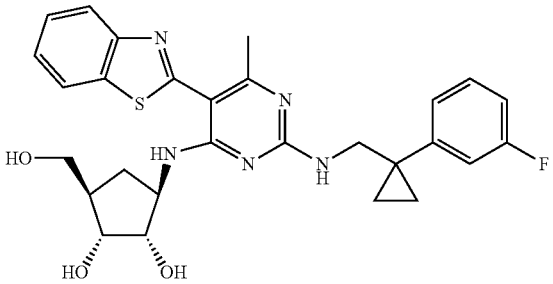
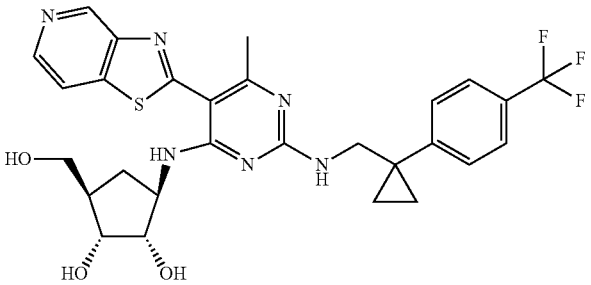
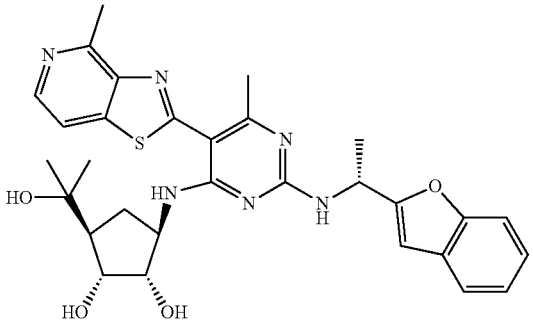
4317	
4504	
4318	
4408	
4514	

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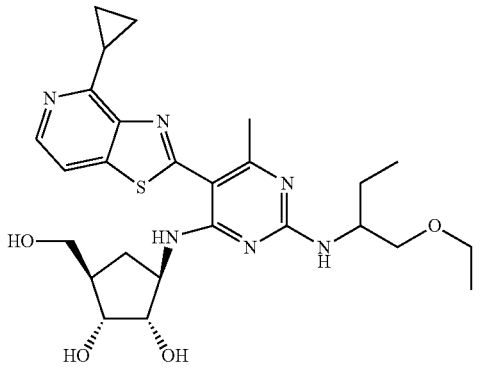
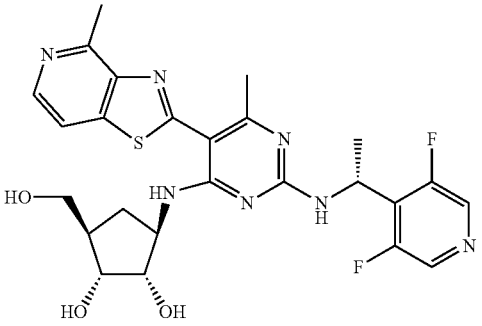
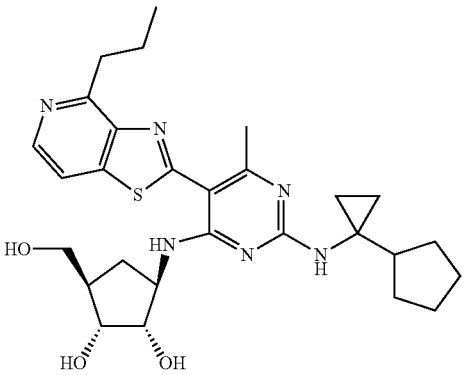
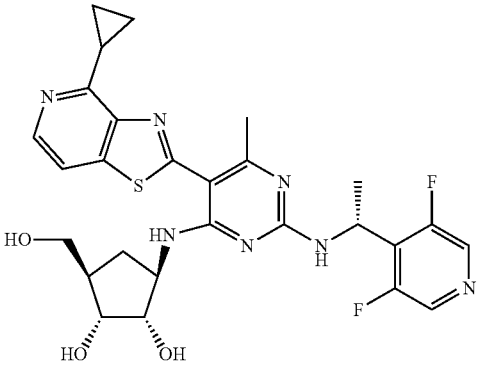
4419	
4525	
4430	
4526	

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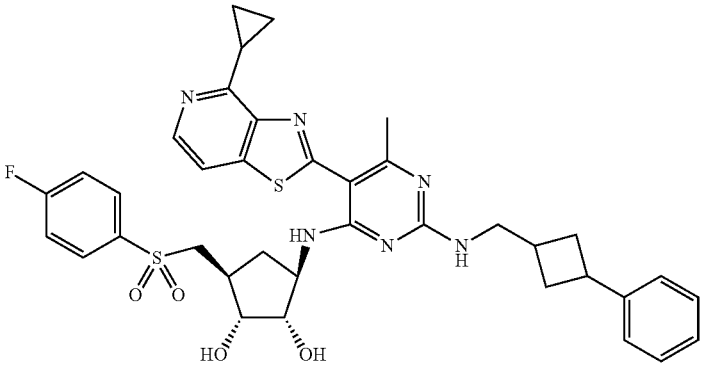
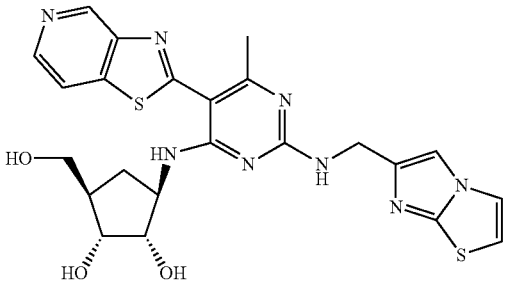
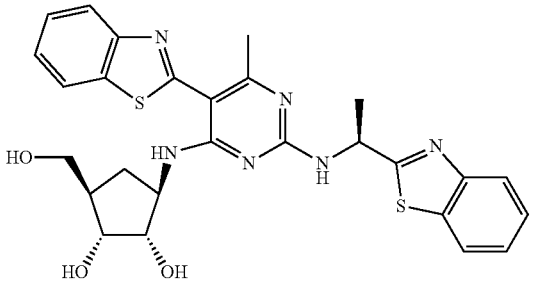
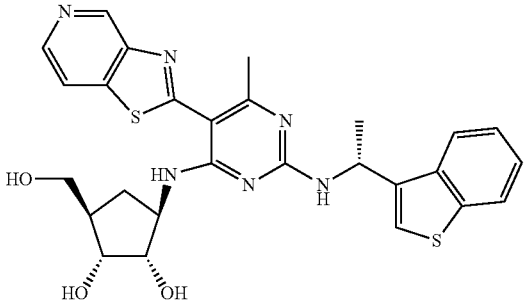
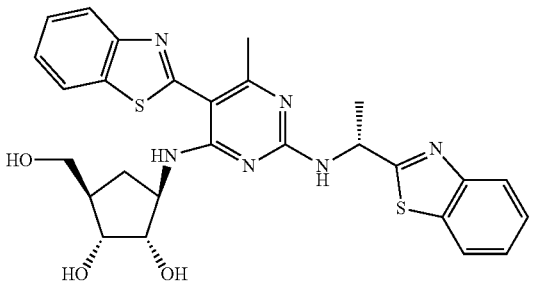
4529	
4612	
4604	
4613	
4605	

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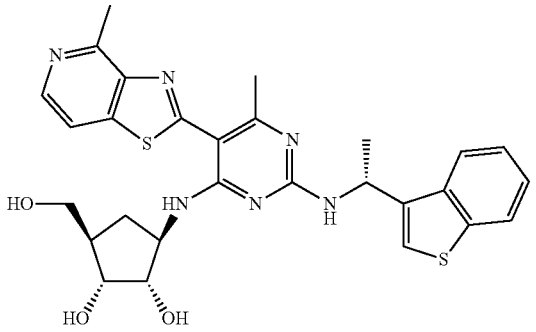
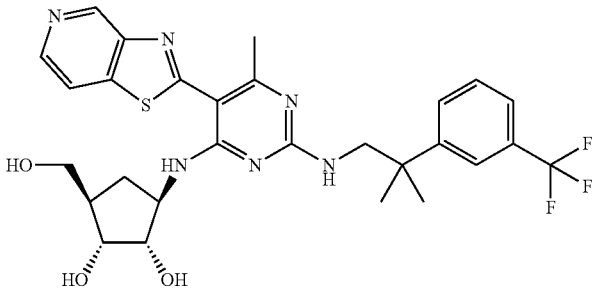
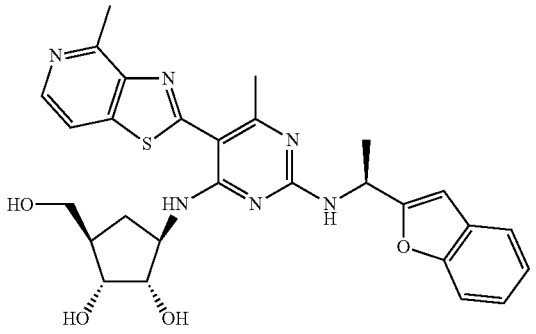
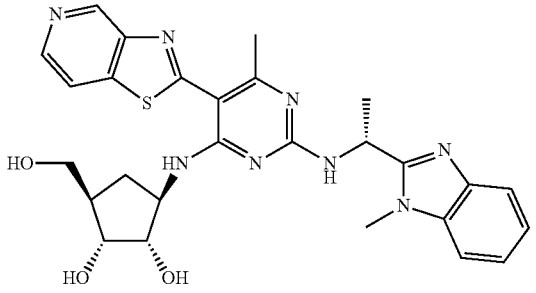
4617	
4606	
4620	
4609	

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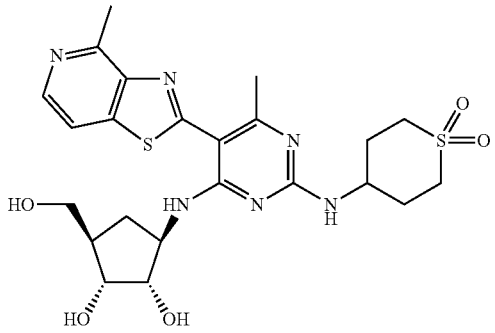
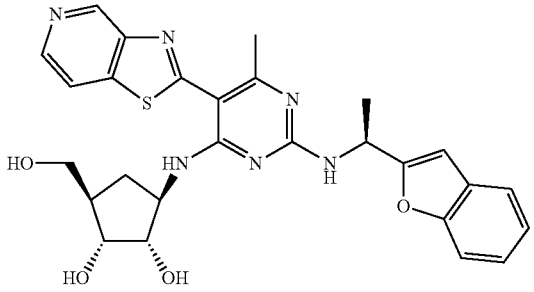
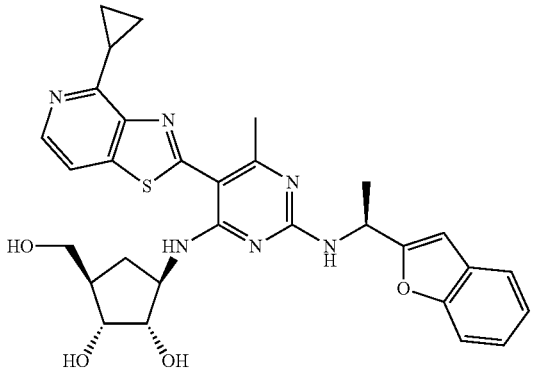
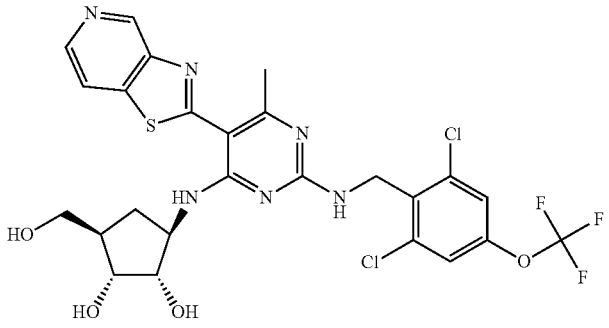
4622	
4610	
4630	
4709	

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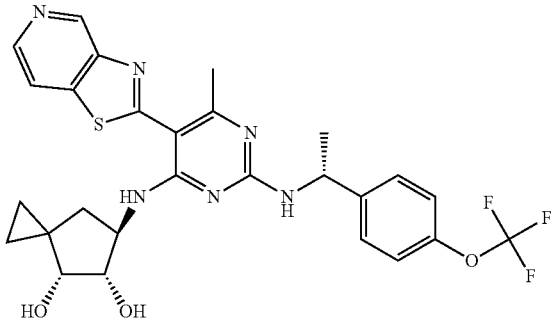
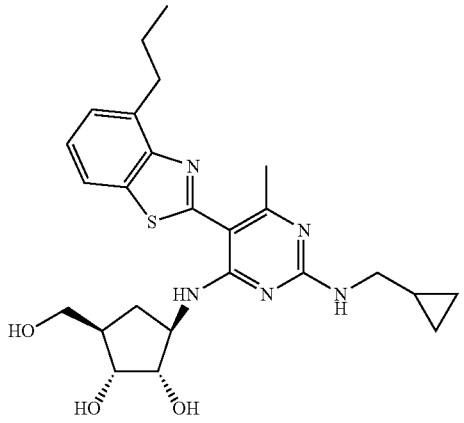
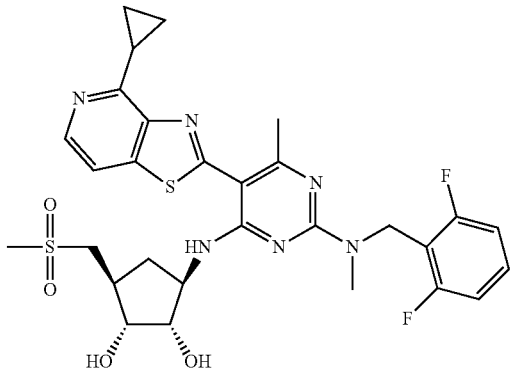
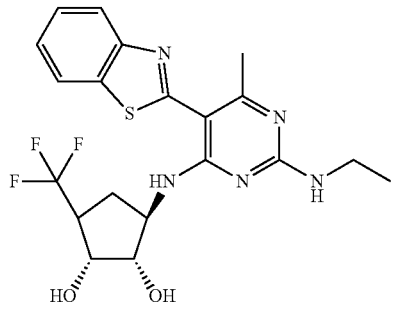
4710	
4720	
3599	
3002	

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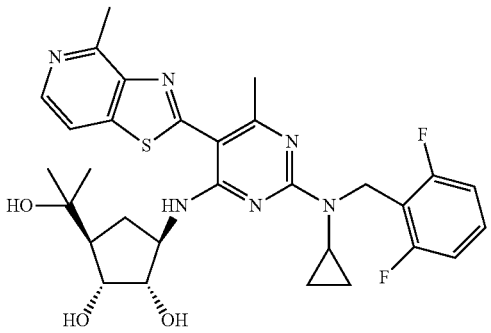
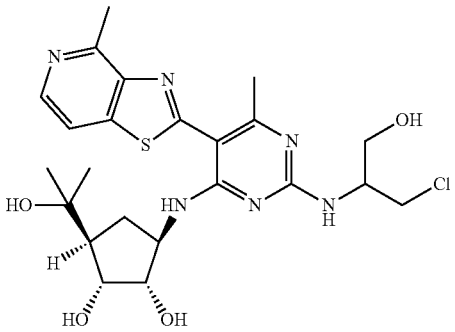
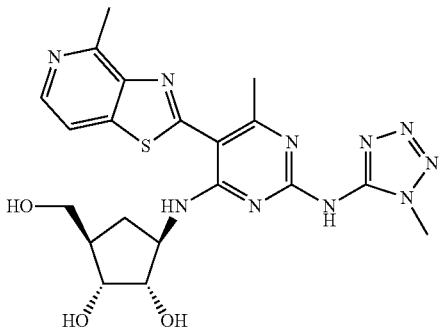
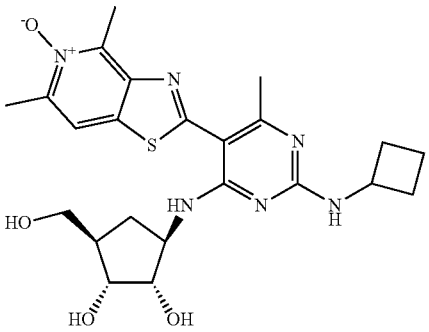
3601	
3172	
4011	
3406	

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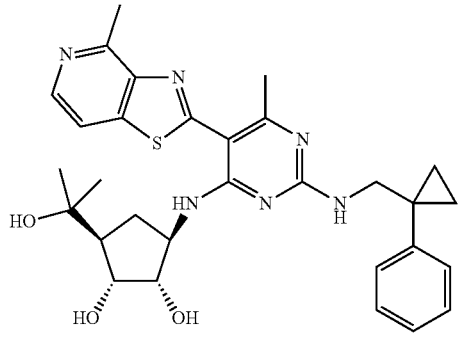
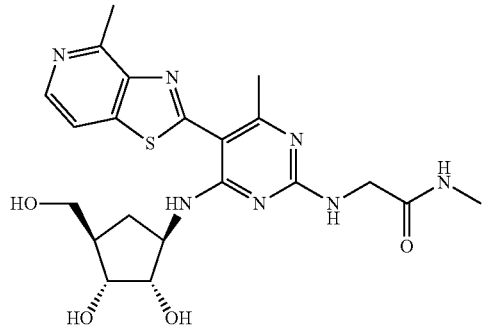
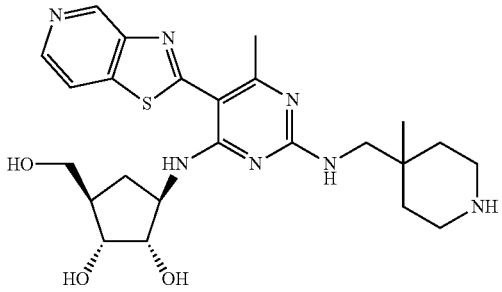
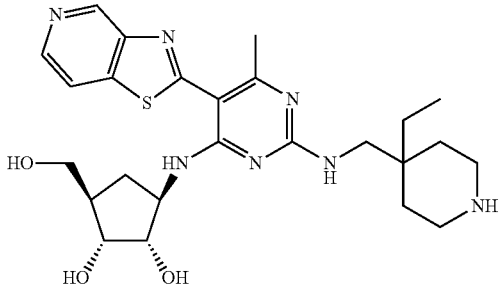
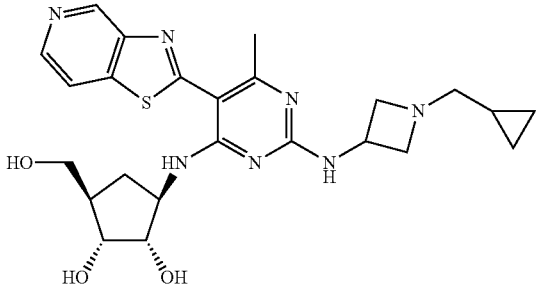
Compd #	Structure
4226	
3429	
4403	
4402	
4501	

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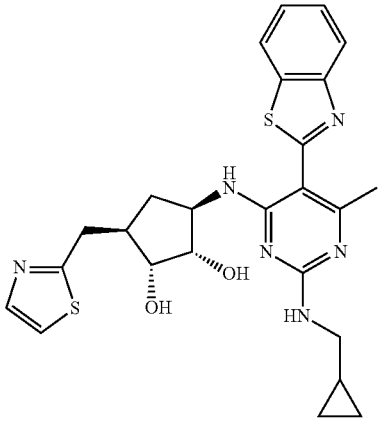
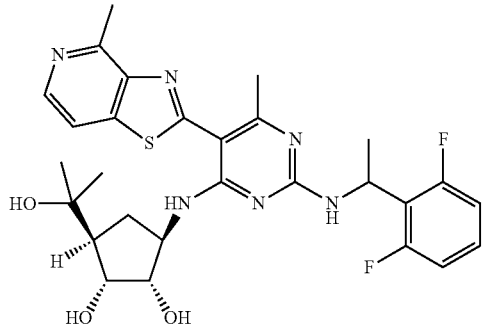
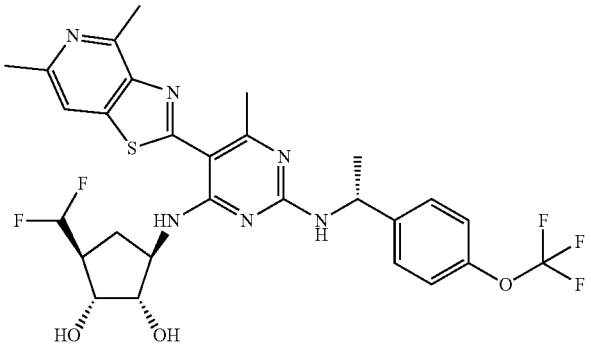
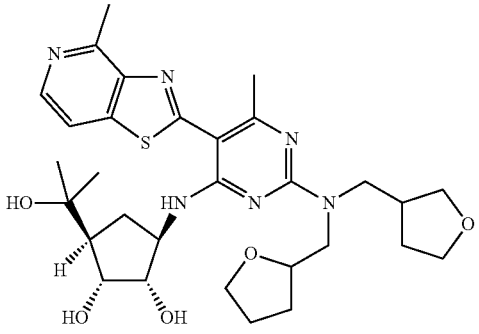
4725	
3150	
3409	
3196	

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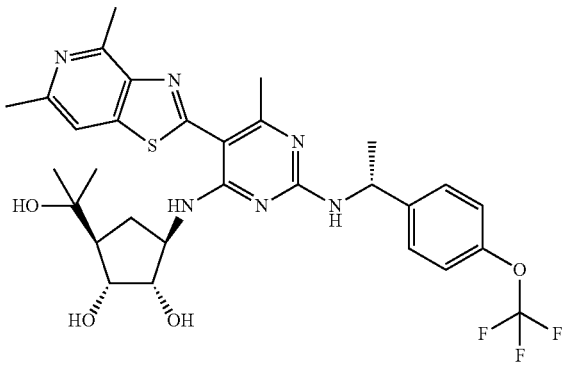
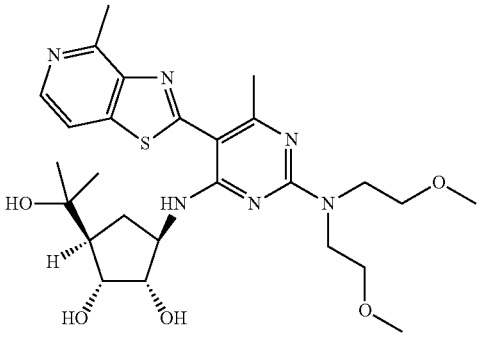
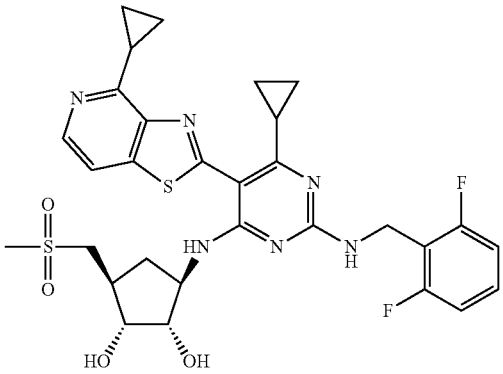
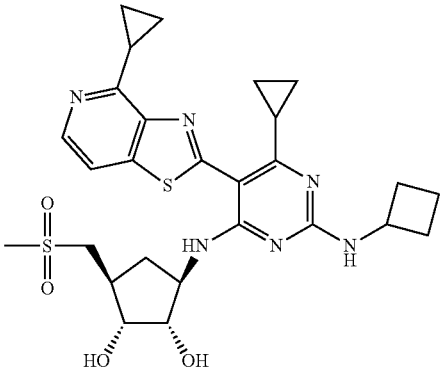
3424	
3237	
3588	
3589	

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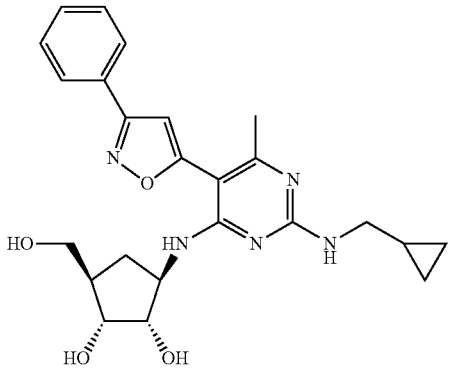
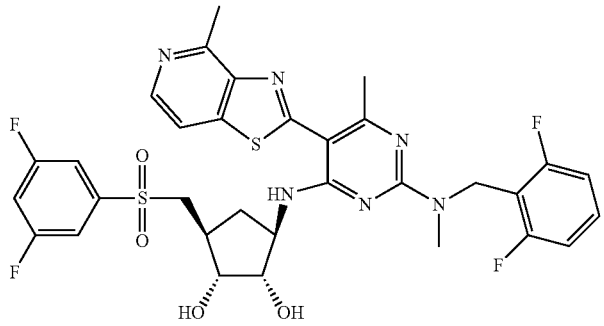
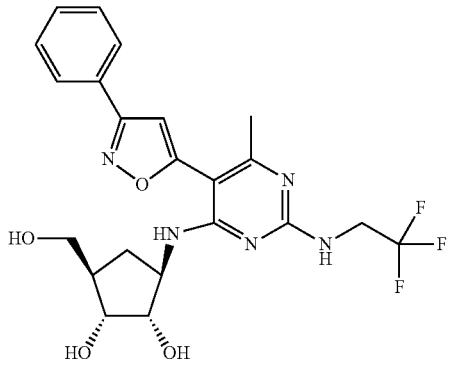
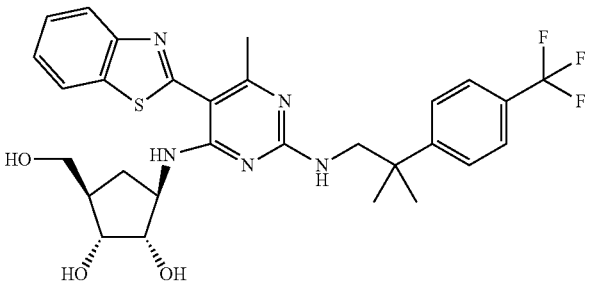
4103	
3598	
4104	
3805	

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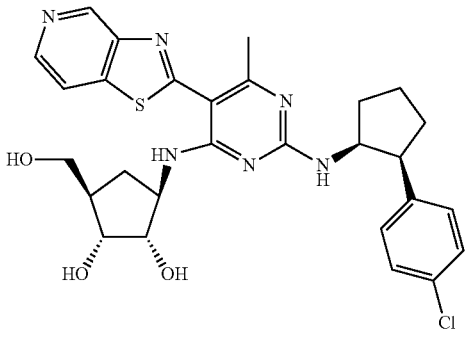
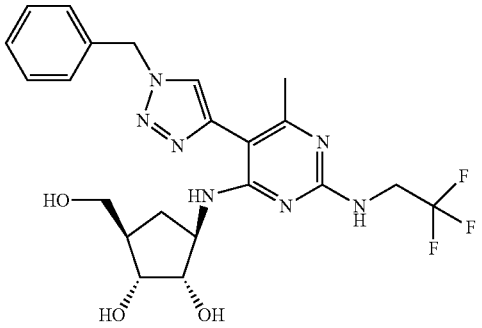
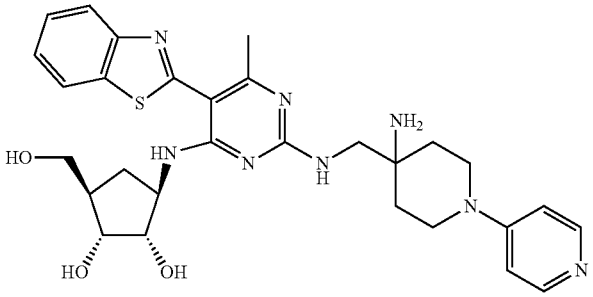
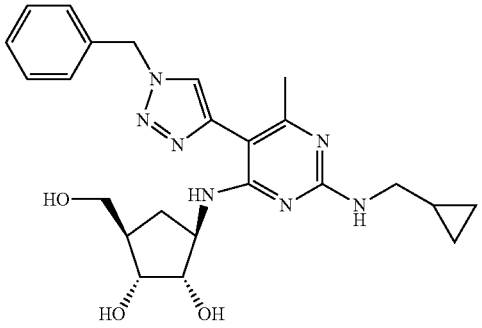
4108	
4101	
4110	
4102	

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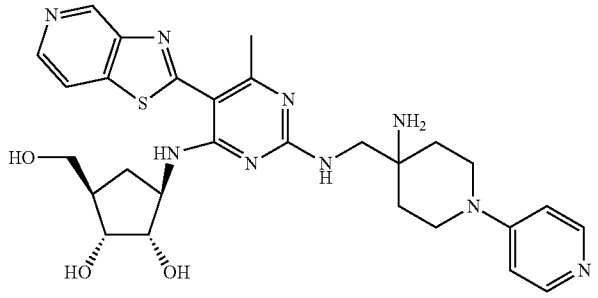
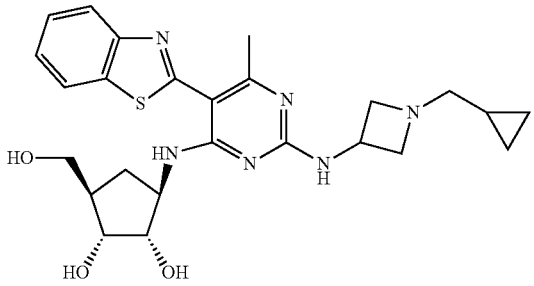
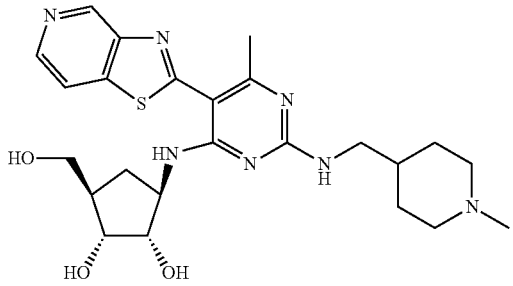
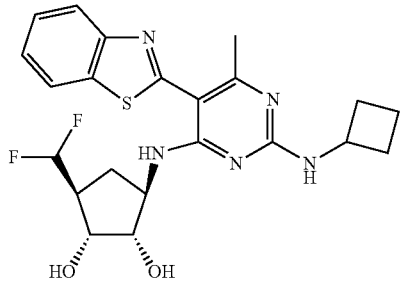
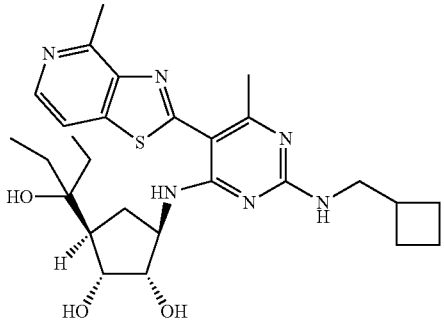
4111	
4502	
4401	
3009	
3221	

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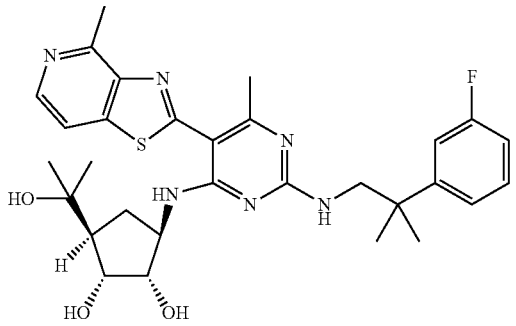
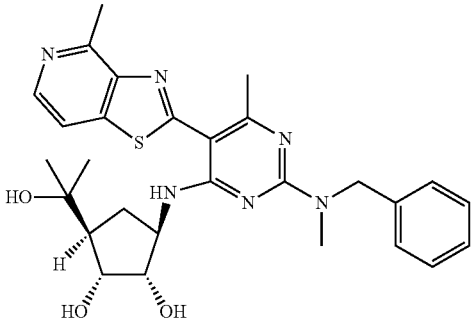
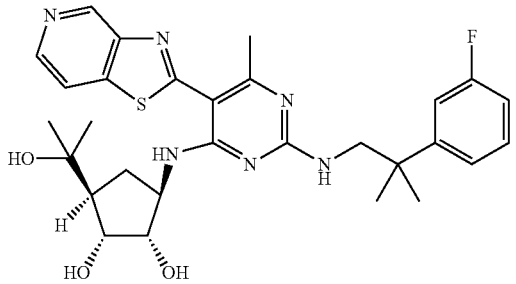
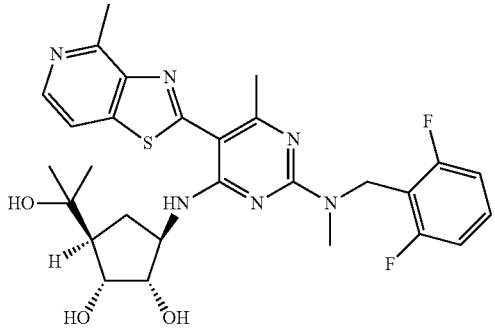
3124	
3234	
3131	
3238	

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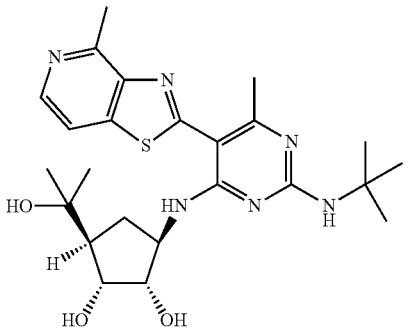
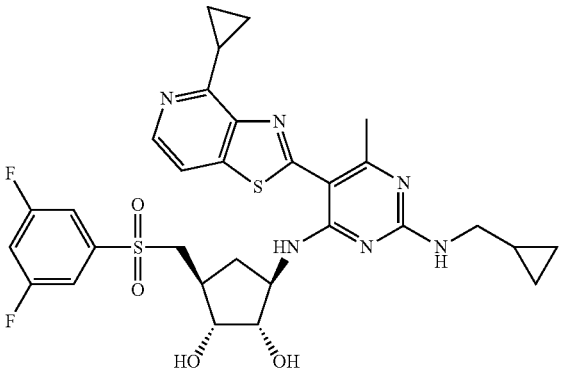
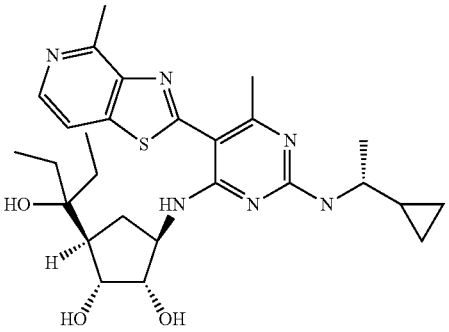
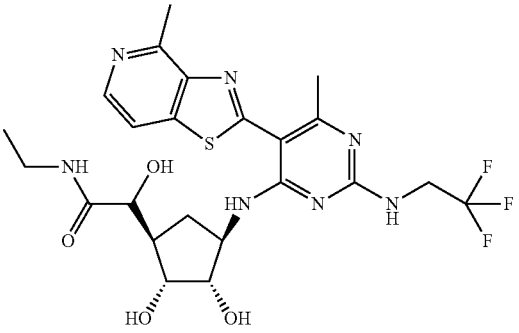
Compd #	Structure
3134	
3572	
3184	
4022	

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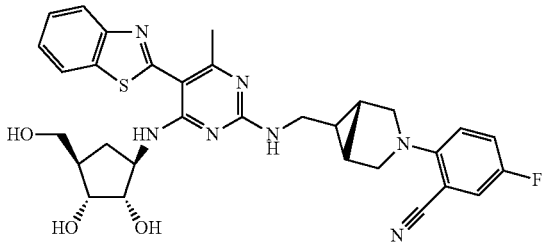
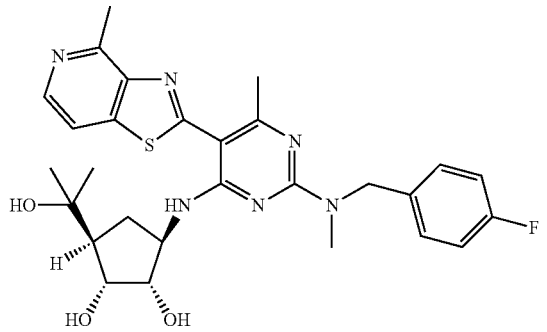
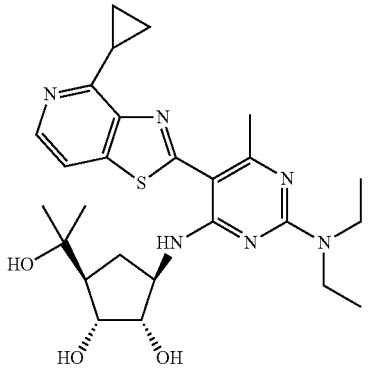
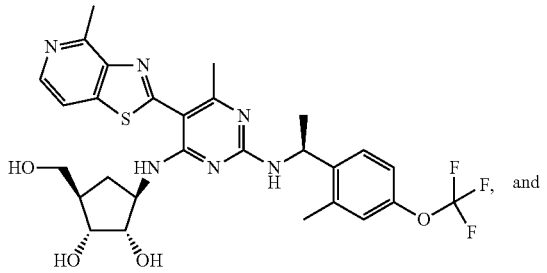
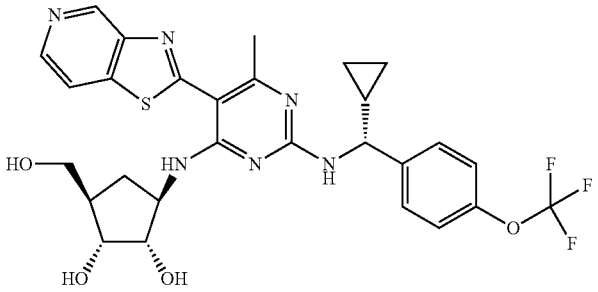
Compd #	Structure
4202	
3232	
4215	
3716	 and
4313	

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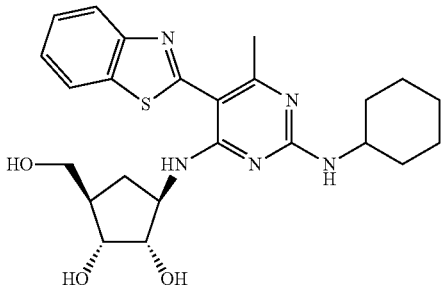
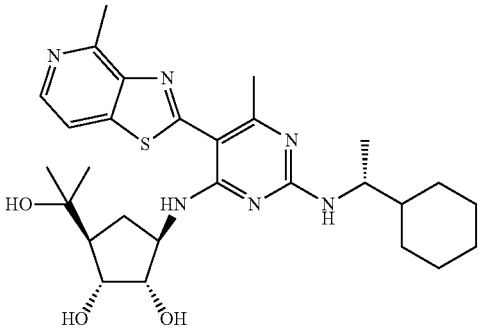
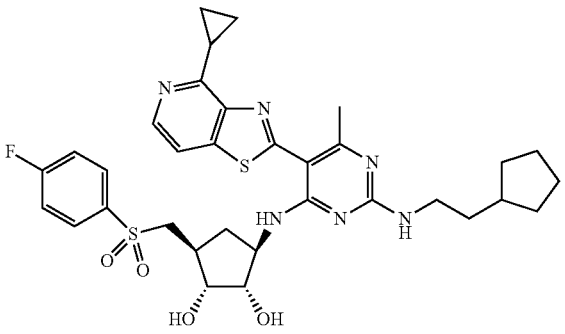
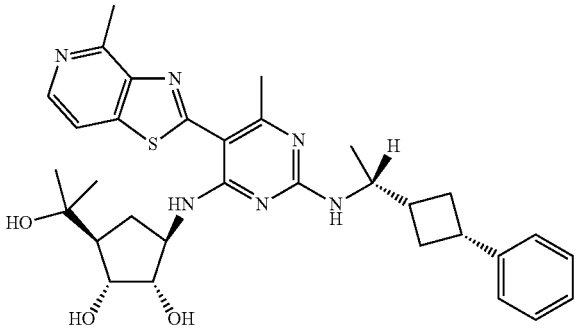
4314	
4423	
4528	
4519	

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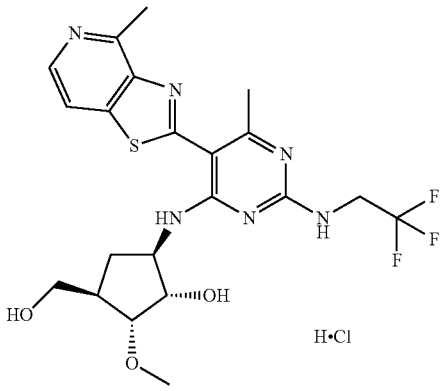
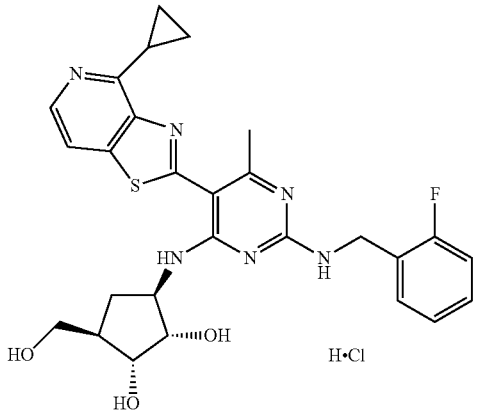
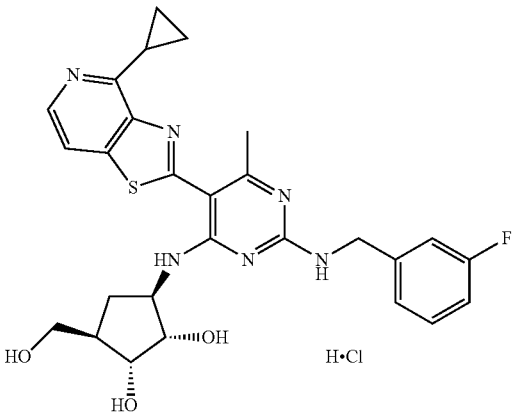
Compd #	Structure
4905	
4901	
4902	

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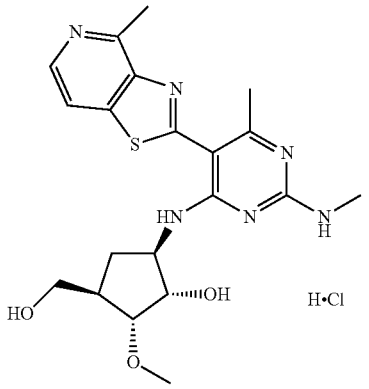
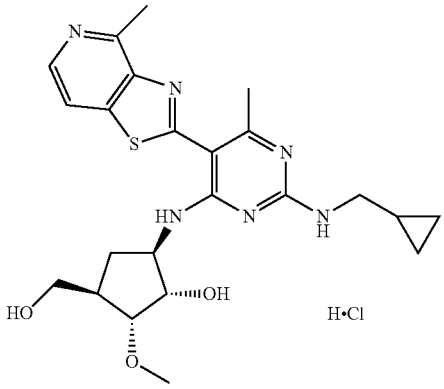
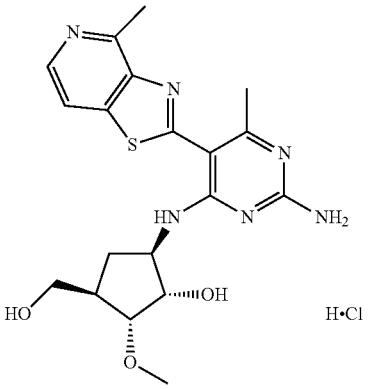
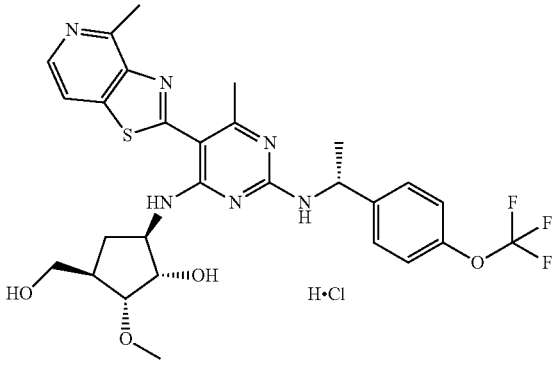
4906	
4903	
4907	
4904	

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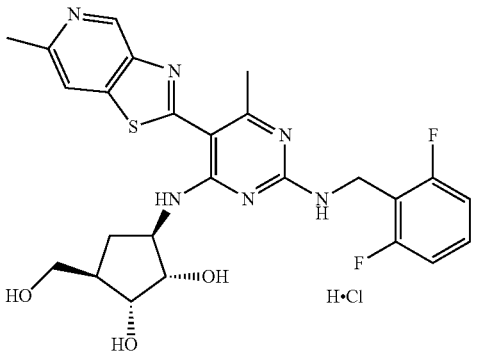
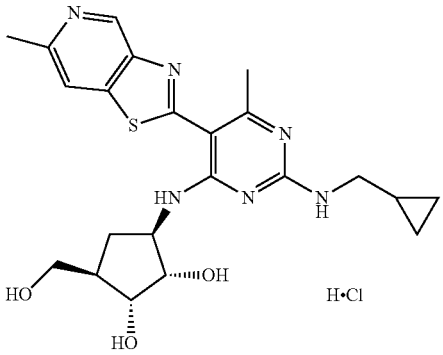
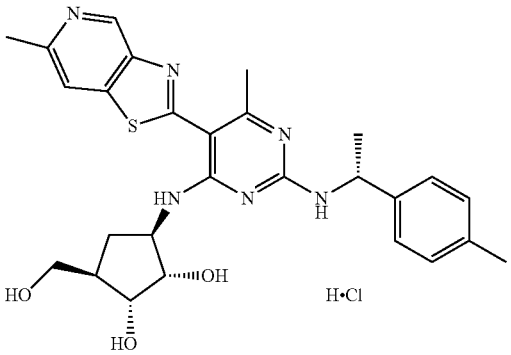
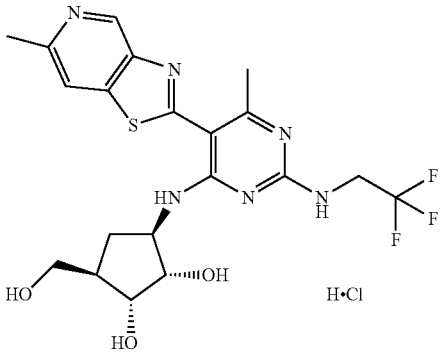
4908	
4909	
4913	
4910	

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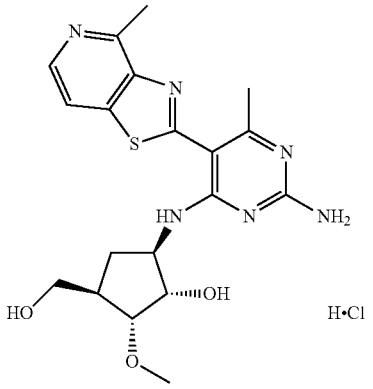
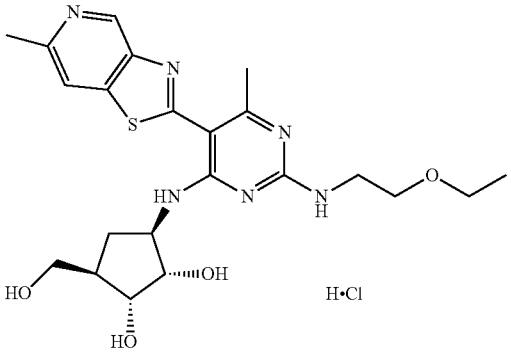
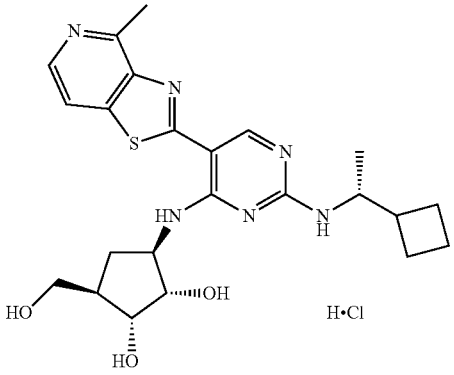
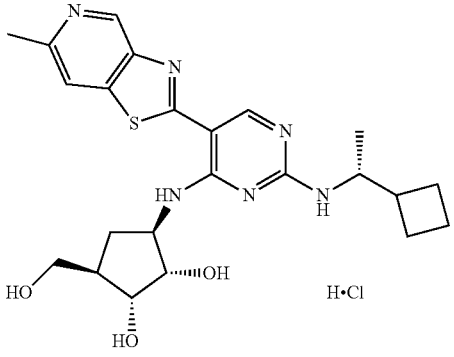
4914	
4911	
4915	
4912	

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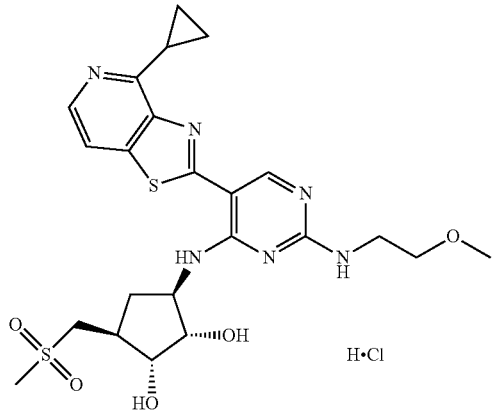
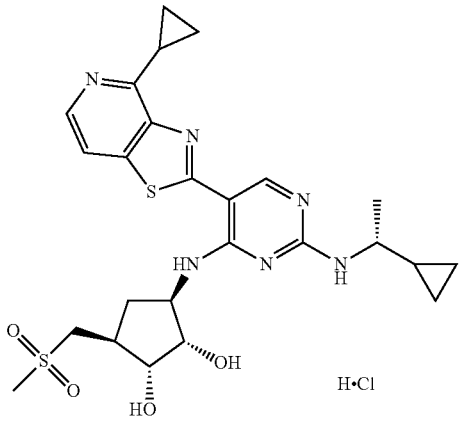
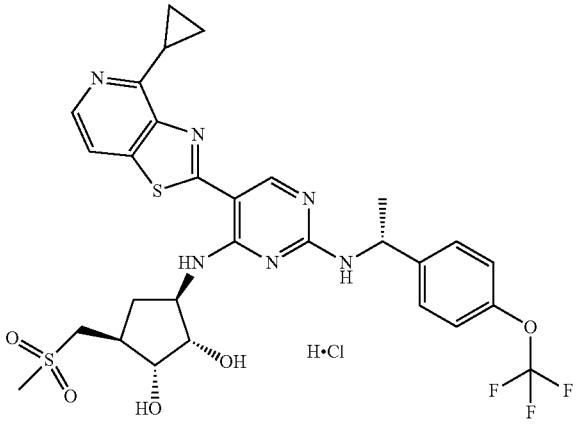
Compd #	Structure
4916	
4917	
4921	

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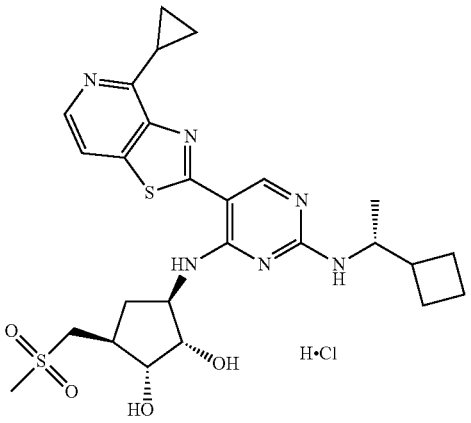
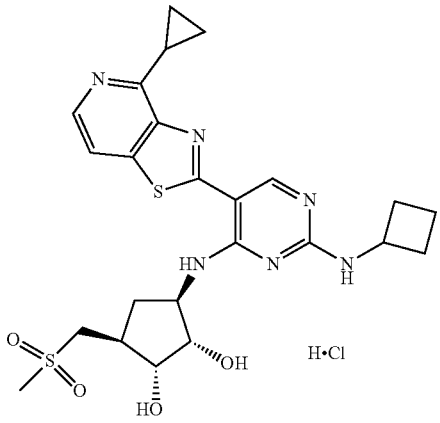
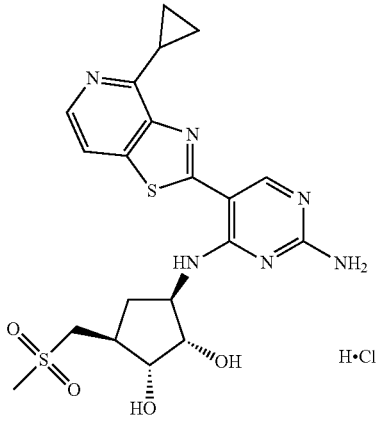
4918	
4922	
4919	

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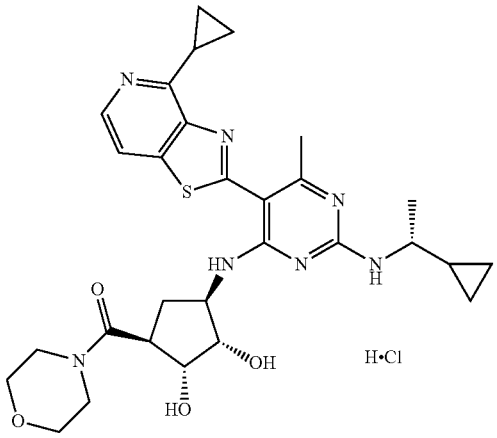
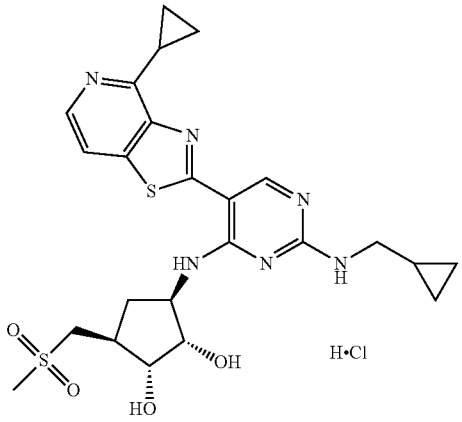
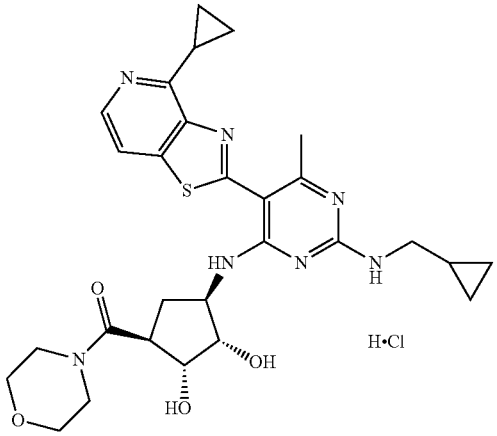
4923	
4920	
4924	

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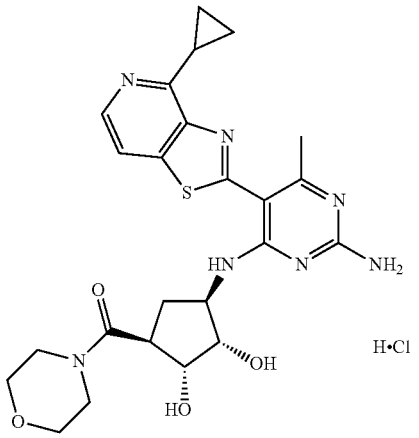
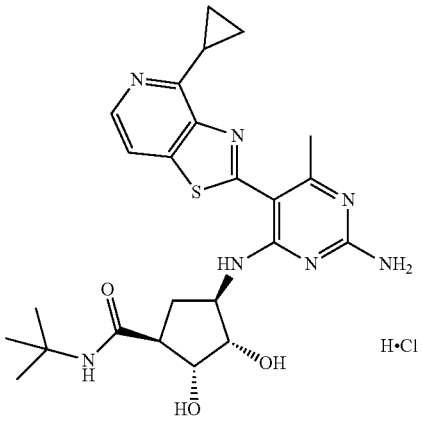
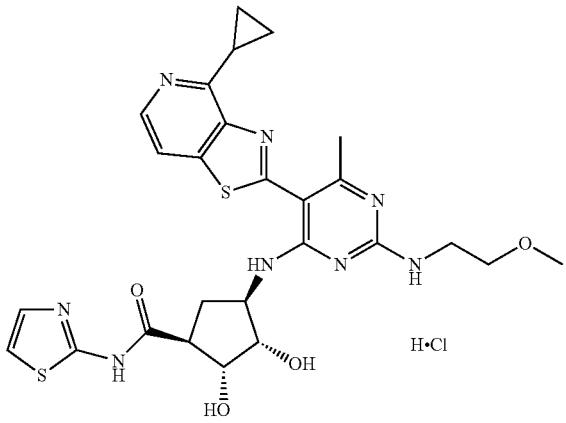
4925	
4929	
4926	

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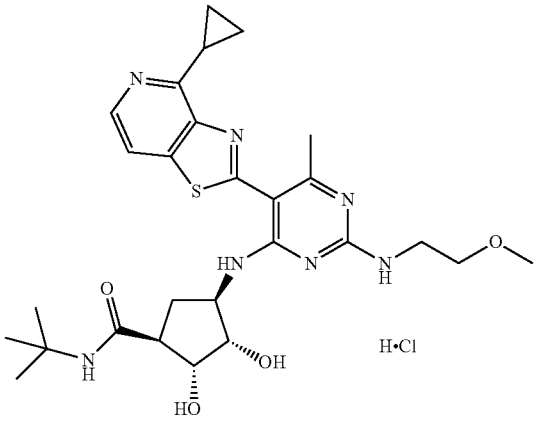
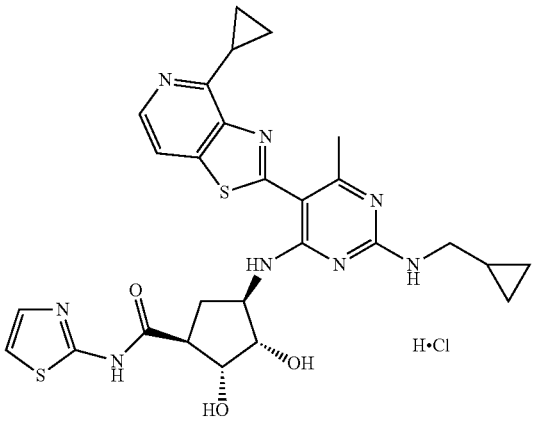
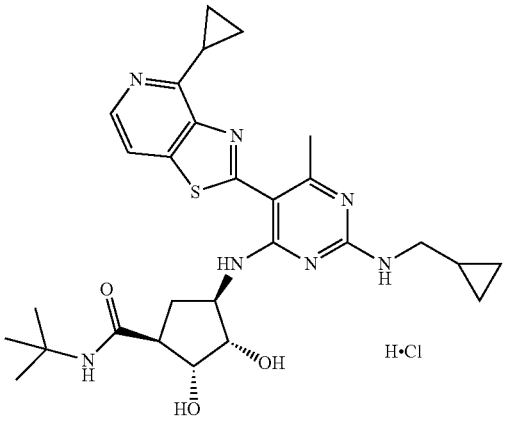
4930	
4927	
4931	

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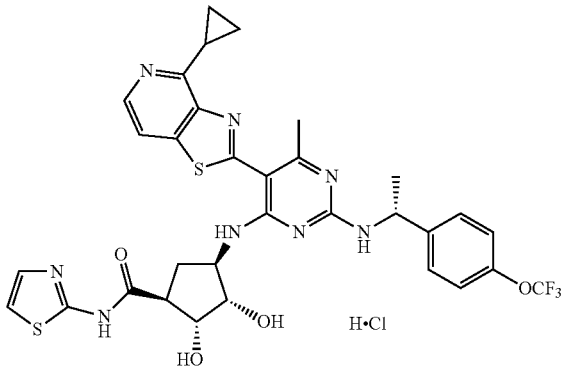
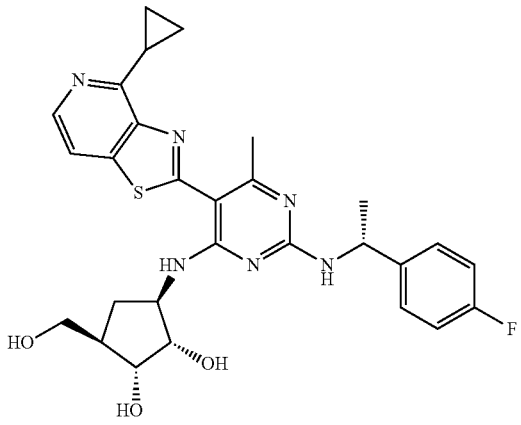
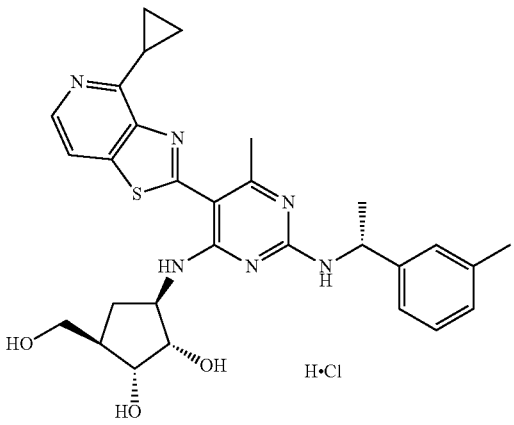
4928	
4932	
4933	

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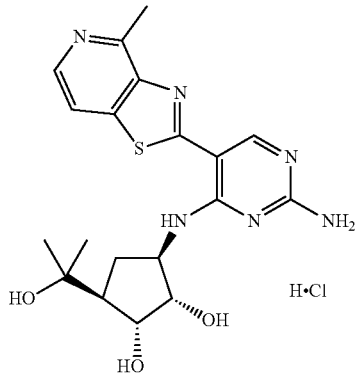
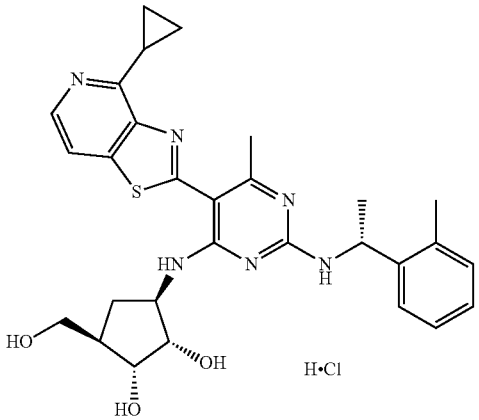
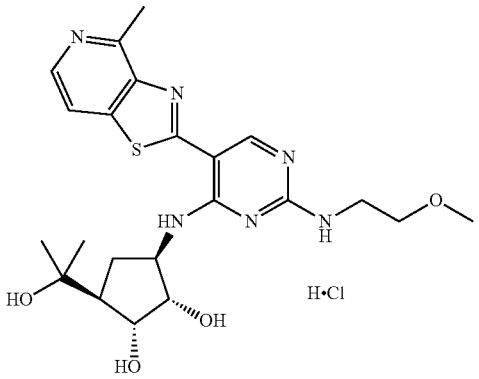
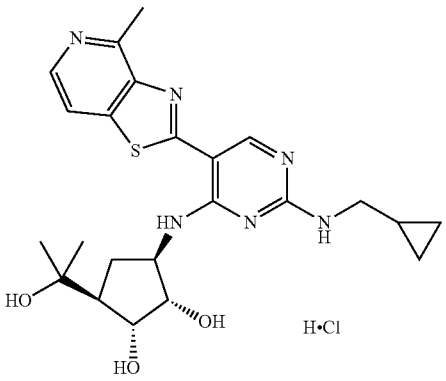
4937	
4934	
4938	
4935	

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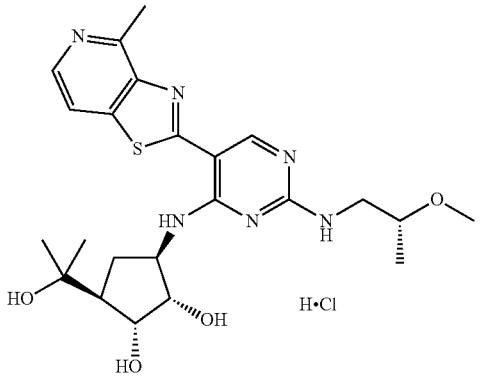
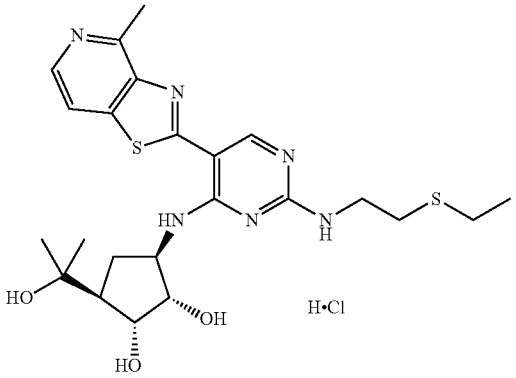
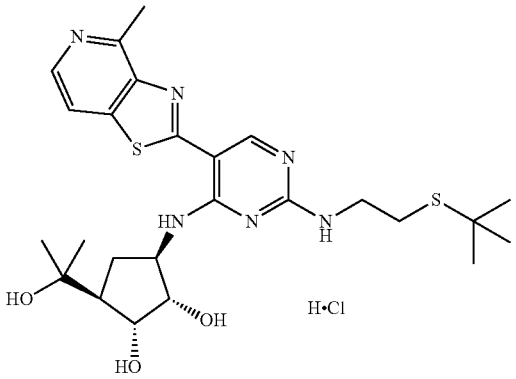
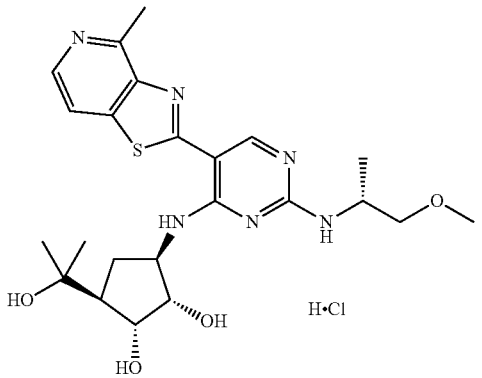
4939	
4936	
4940	
4941	

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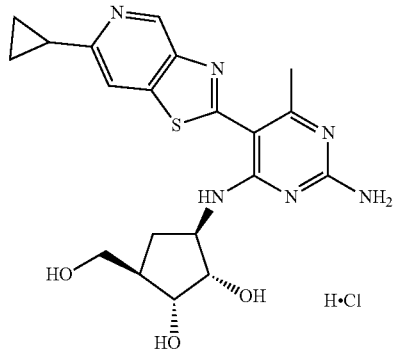
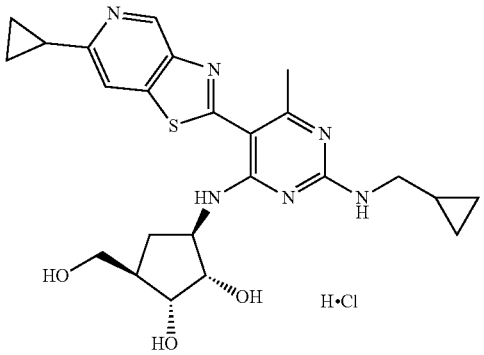
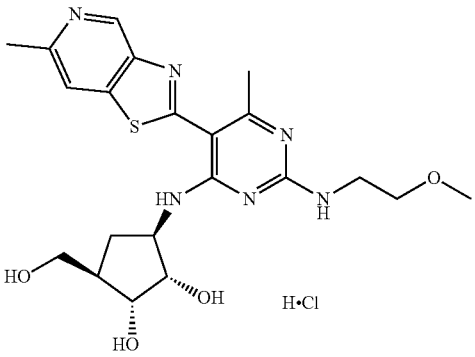
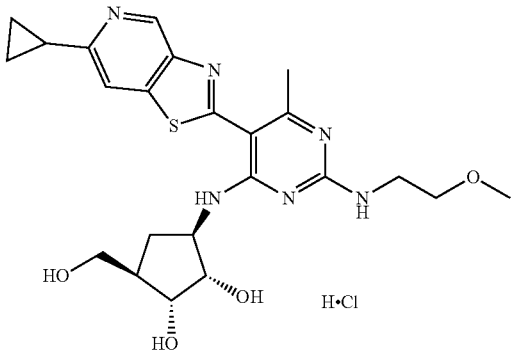
4945	
4942	
4946	
4943	

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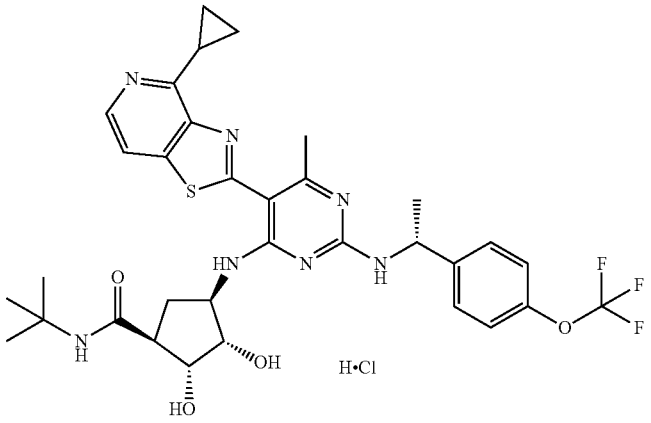
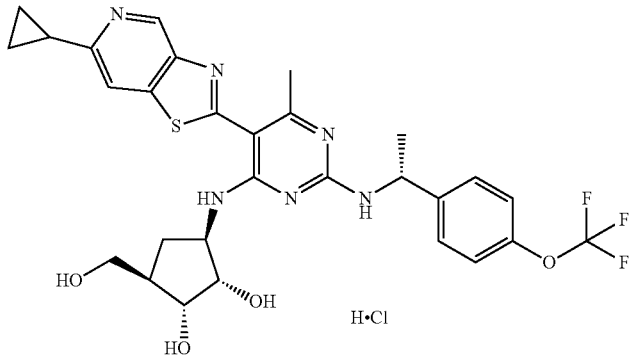
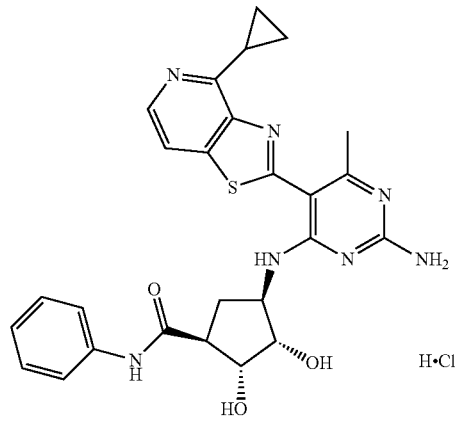
4947	
4944	
4948	

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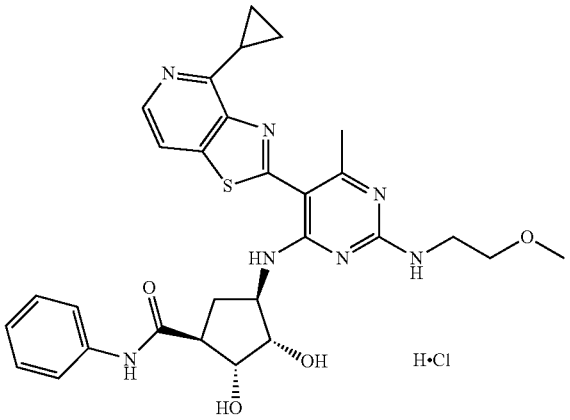
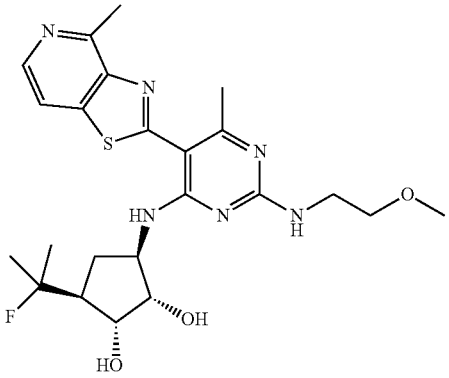
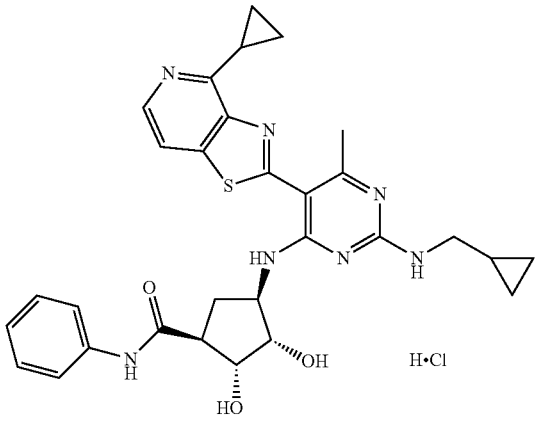
4949	
4954	
4950	

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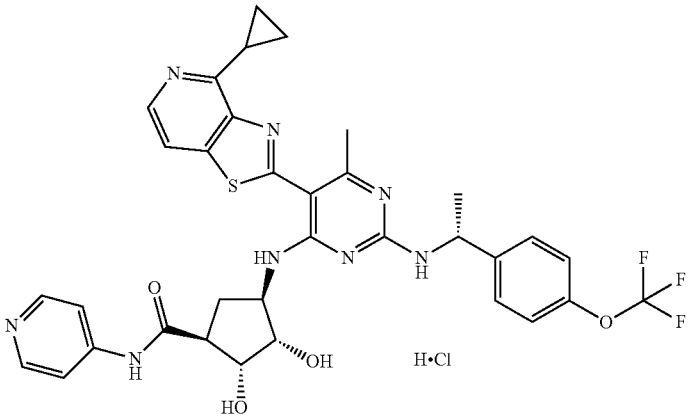
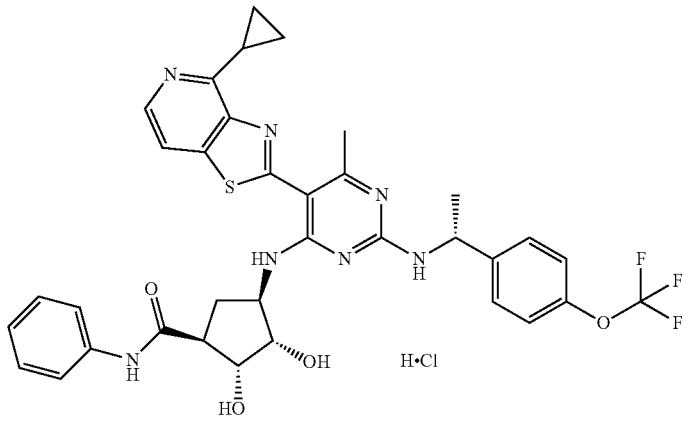
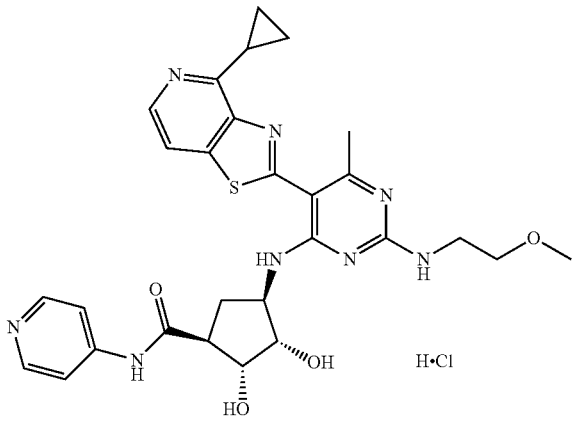
Compd #	Structure
4955	
4951	
4956	

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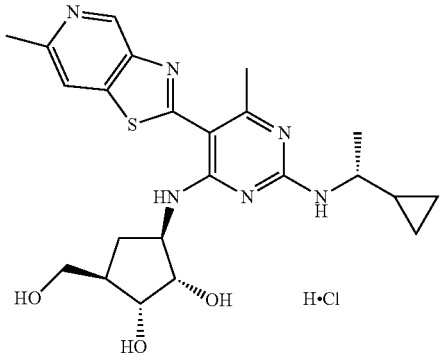
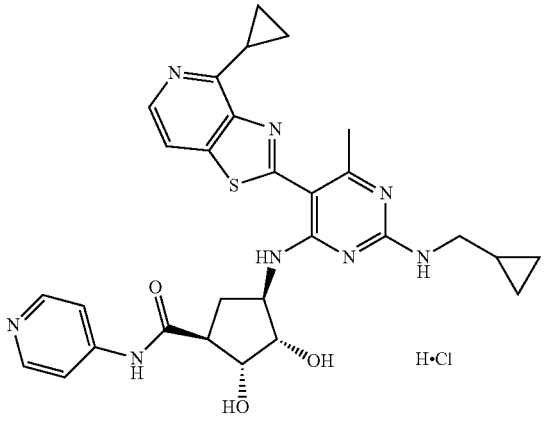
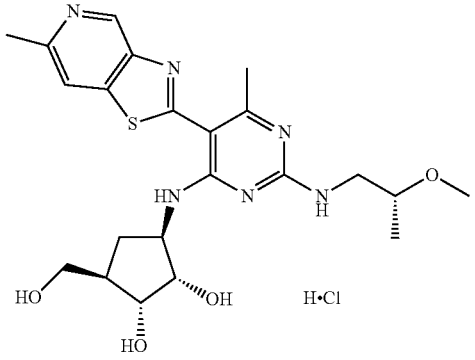
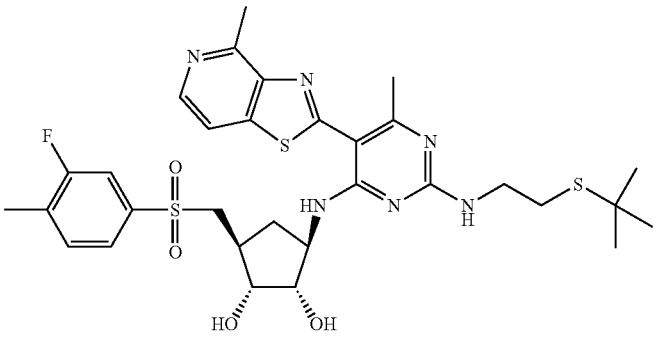
4952	
4957	
4953	
5001	

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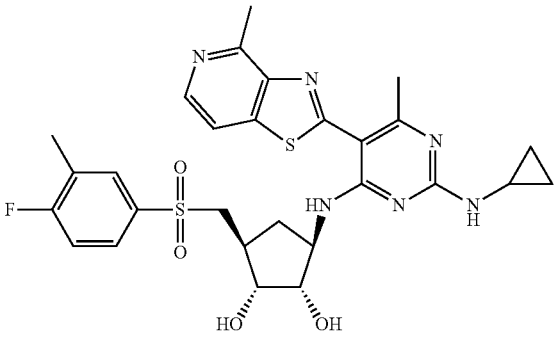
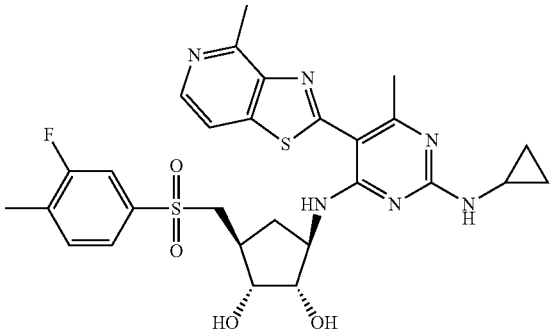
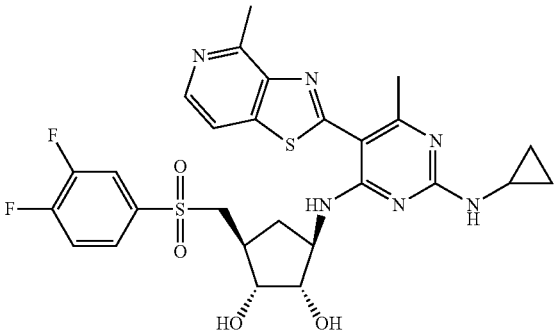
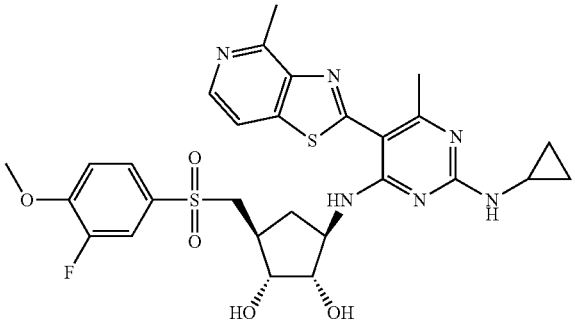
5002	
5003	
5004	
5005	

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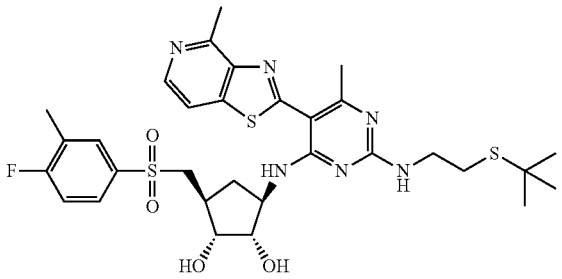
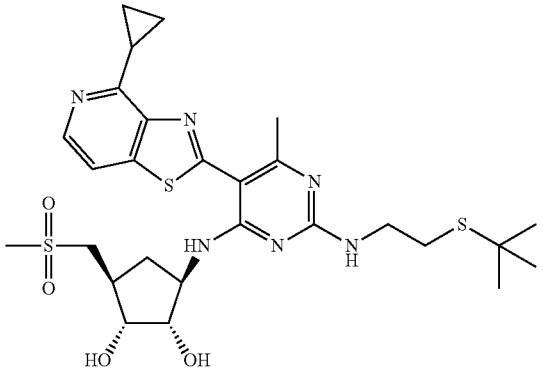
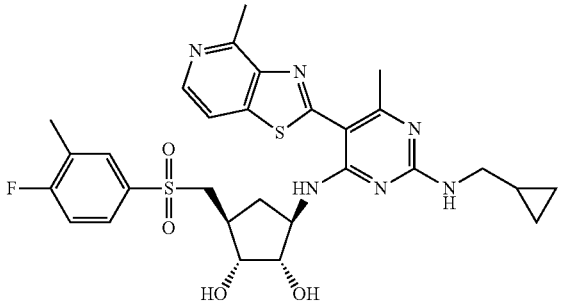
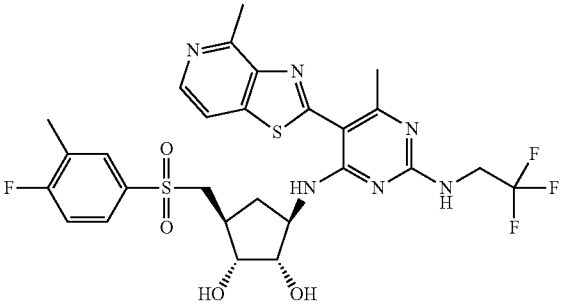
5006	
5007	
5008	
5009	

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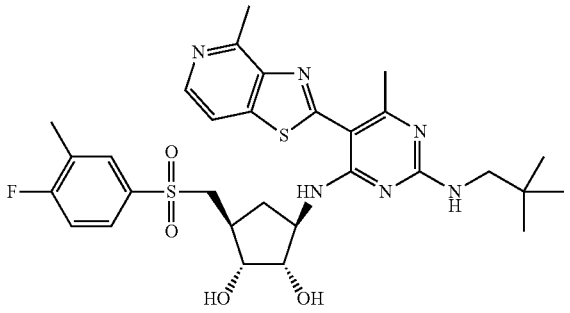
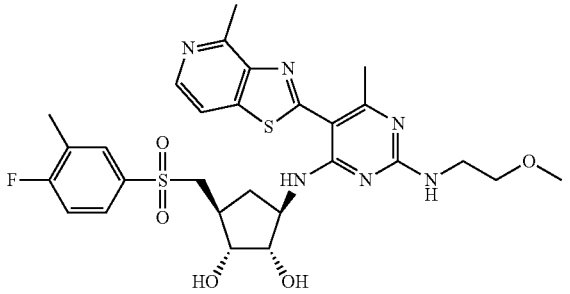
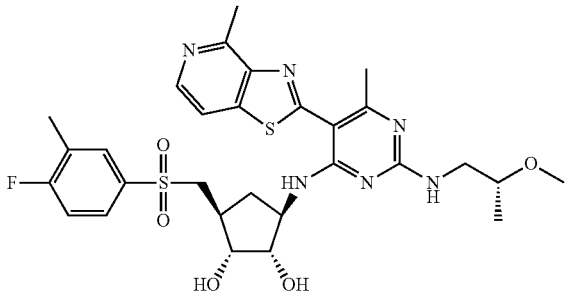
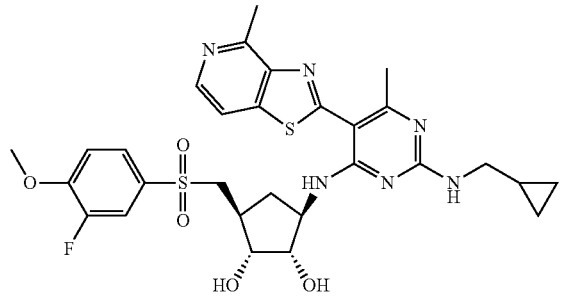
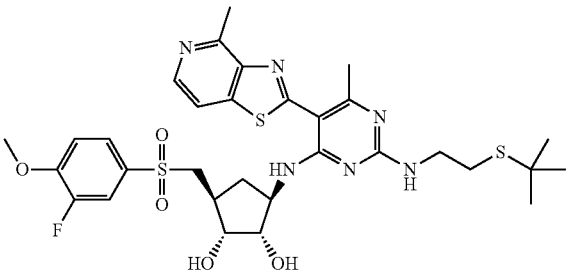
5010	
5011	
5012	
5013	
5014	

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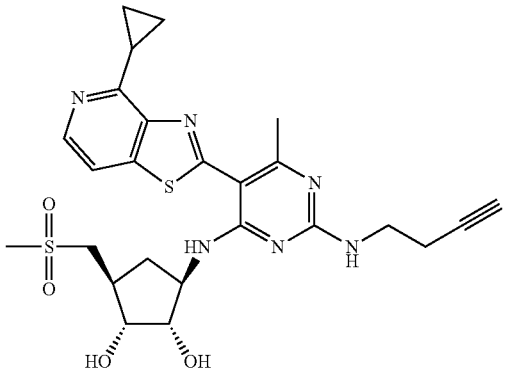
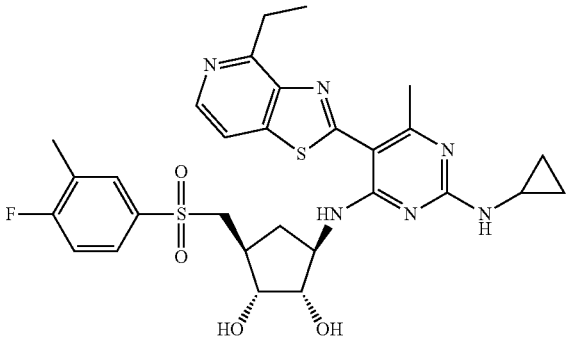
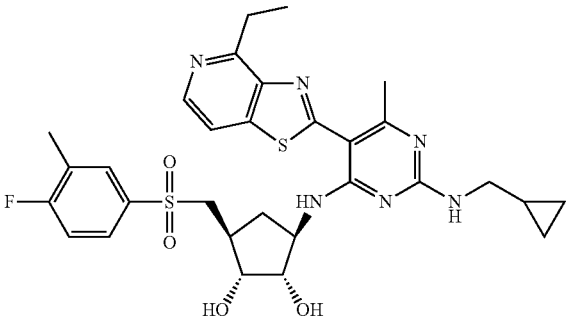
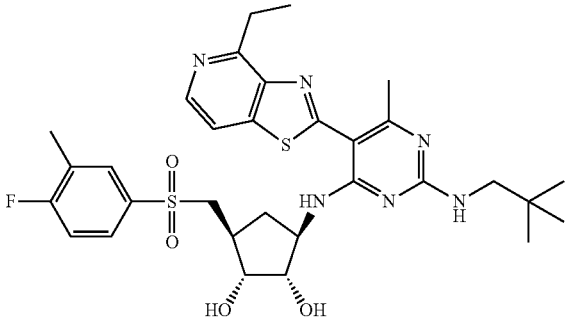
5015	
5016	
5017	
5018	

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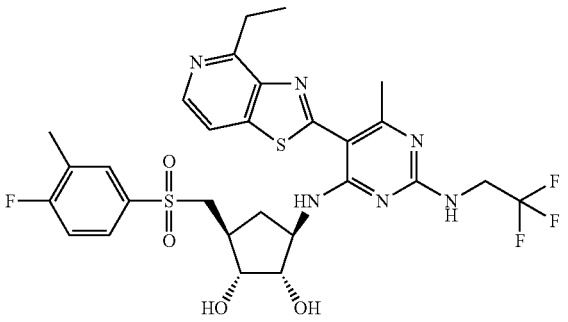
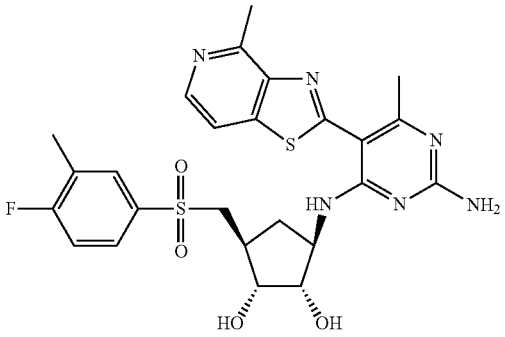
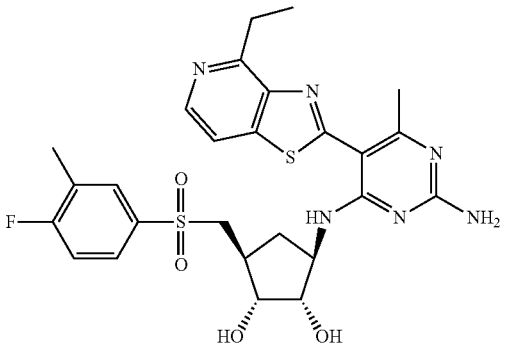
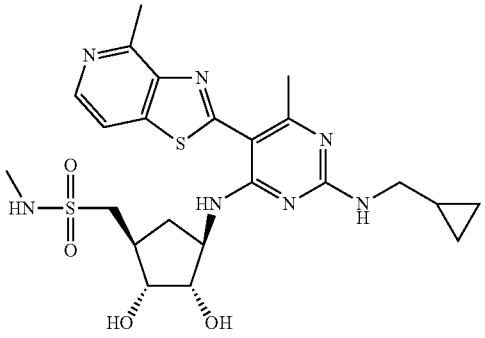
5019	
5020	
5021	
5025	

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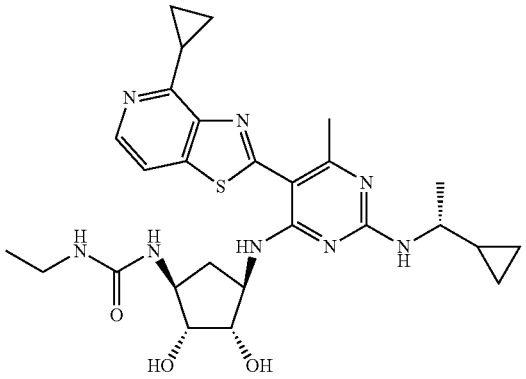
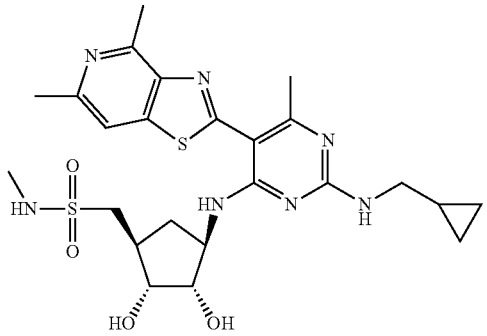
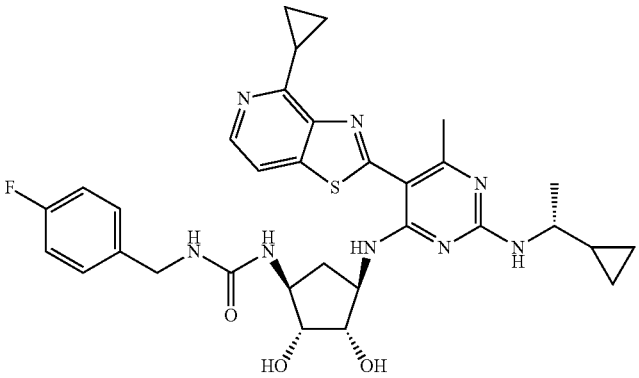
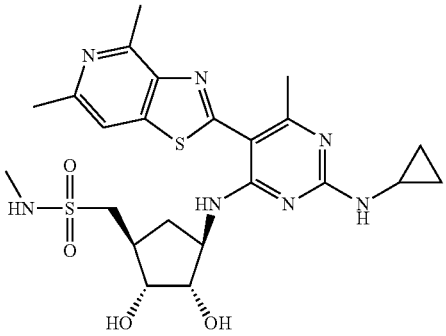
5022	
5026	
5023	
5027	

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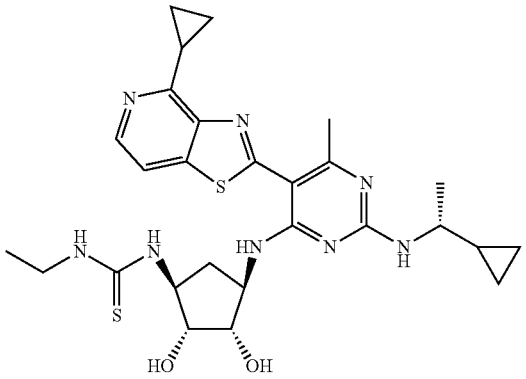
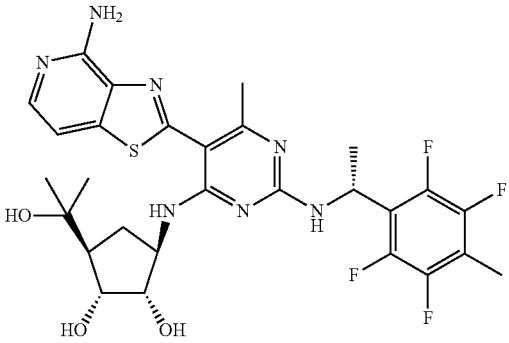
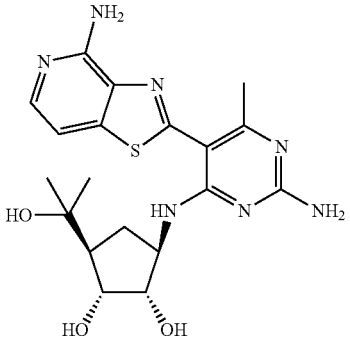
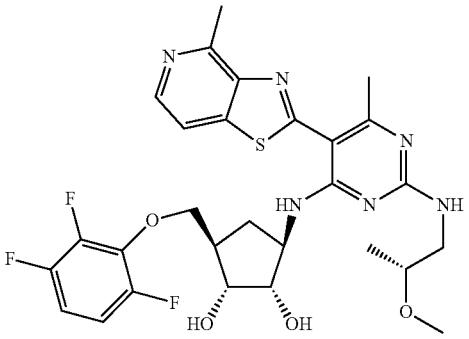
5024	
5028	
5029	
5033	

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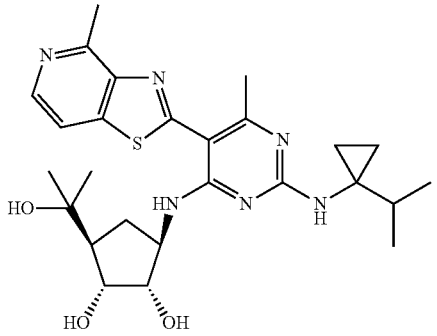
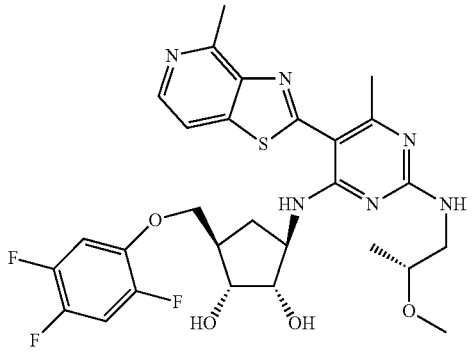
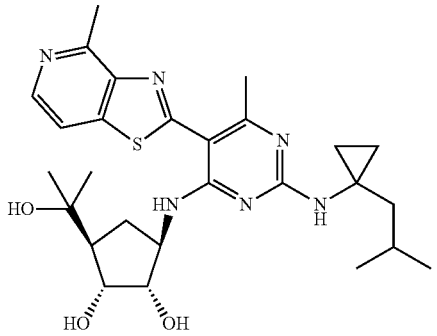
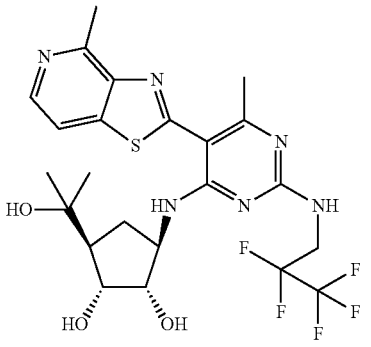
5030	
5034	
5031	
5035	

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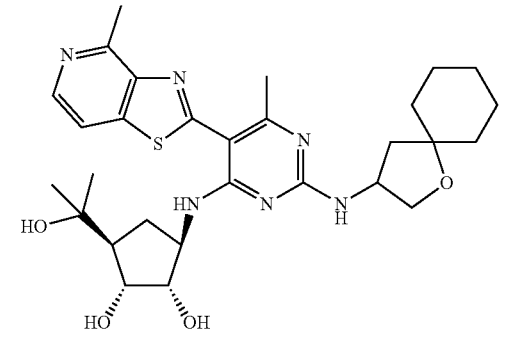
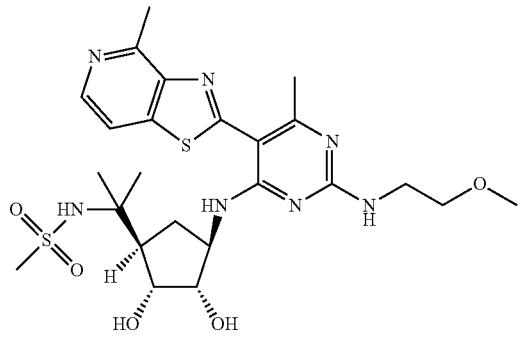
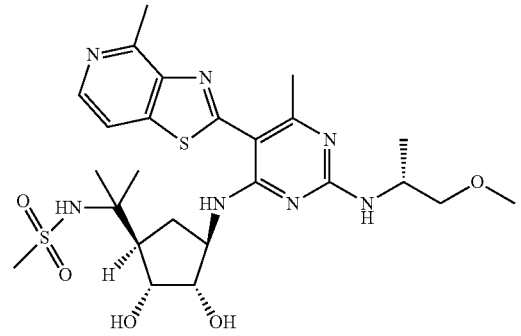
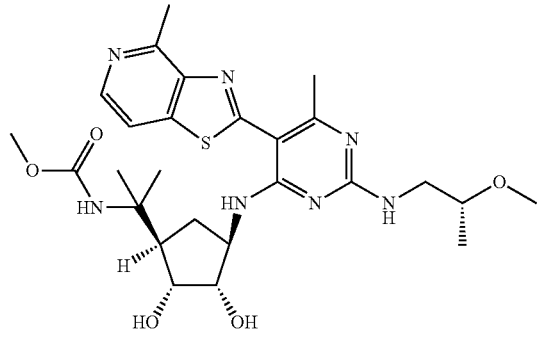
5032	
5036	
5037	
5041	

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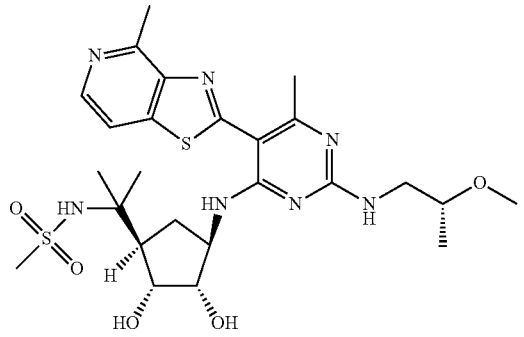
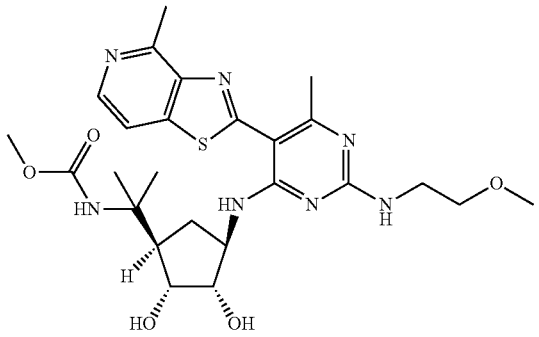
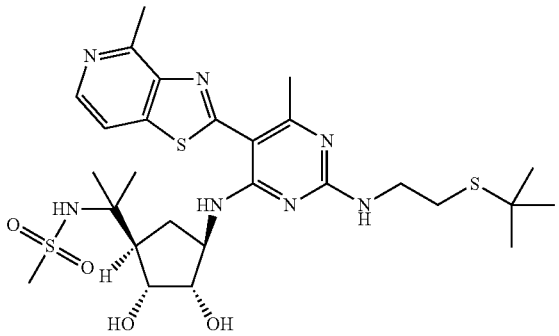
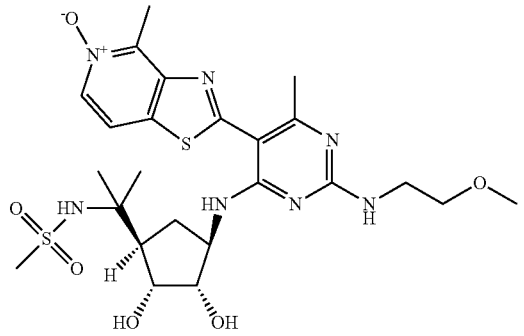
Compd #	Structure
5038	
5042	
5039	
5043	

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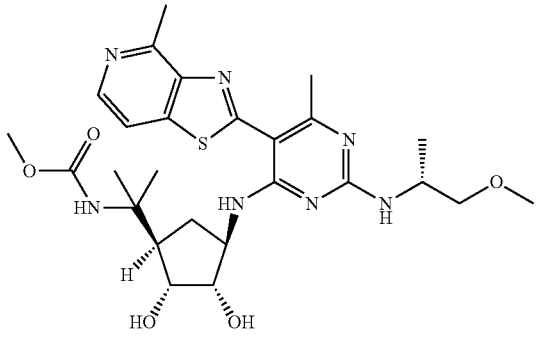
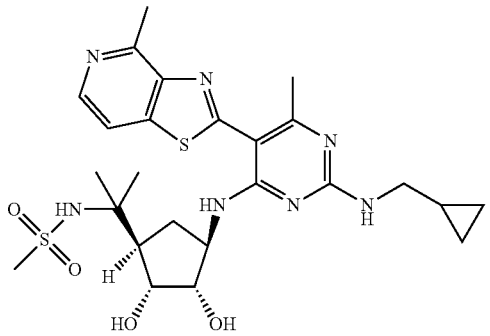
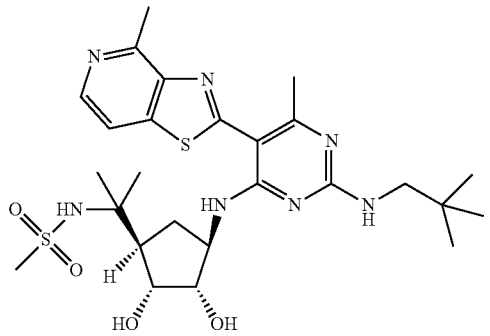
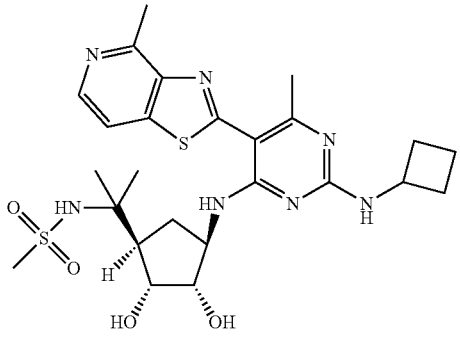
5040	
5044	
5045	
5049	

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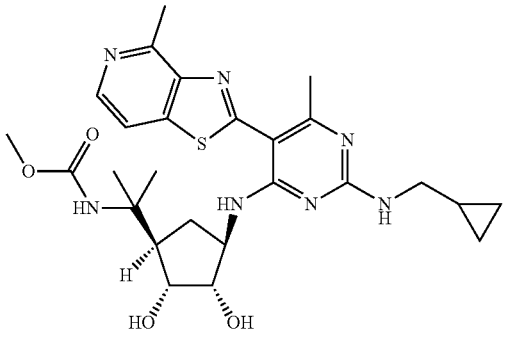
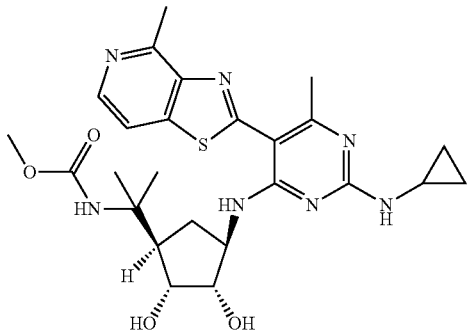
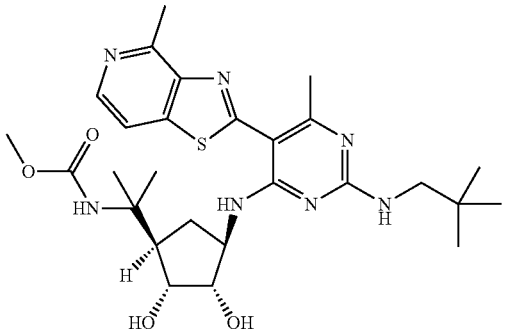
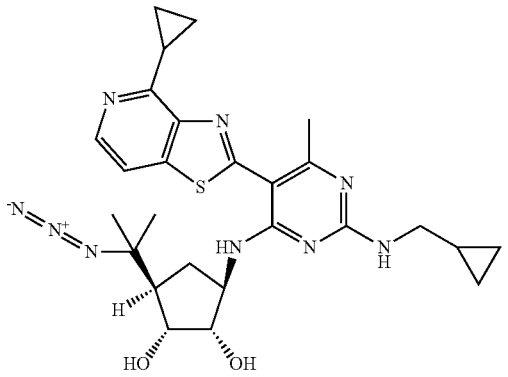
5046	
5050	
5047	
5051	

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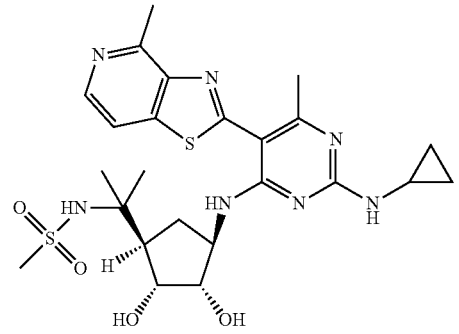
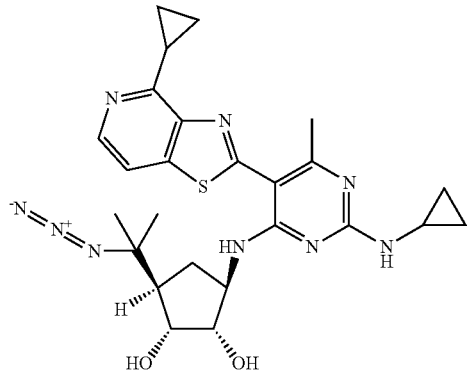
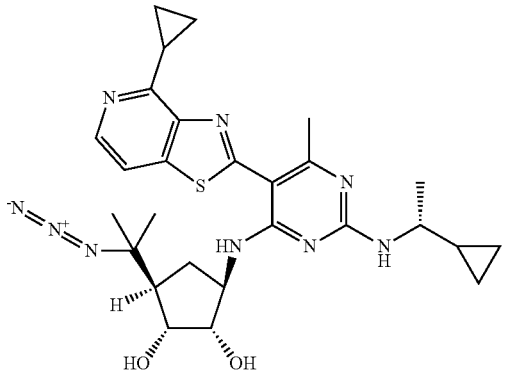
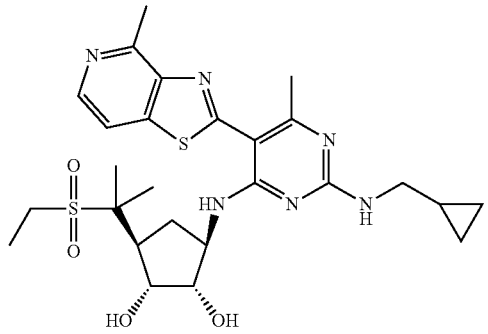
5048	
5052	
5053	
5057	

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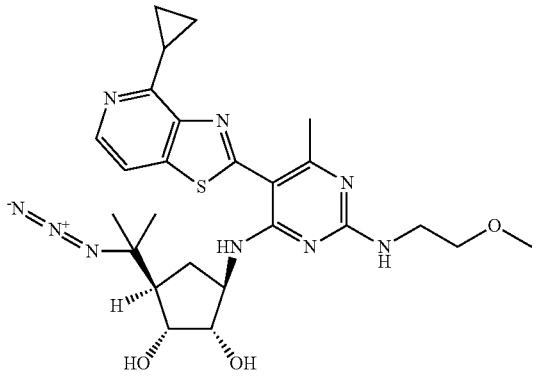
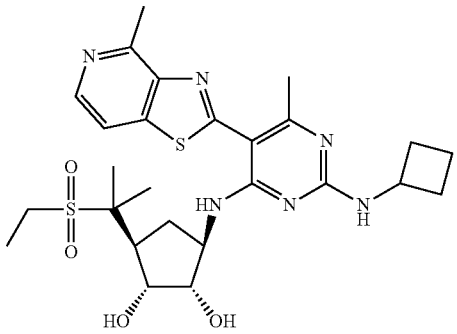
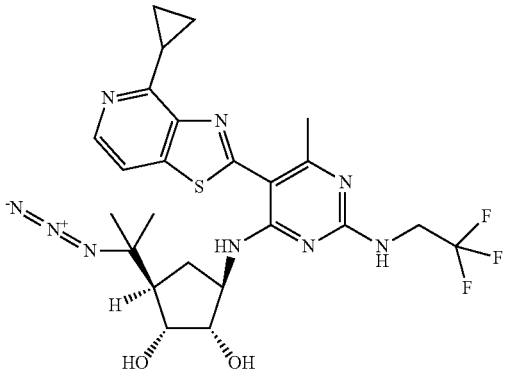
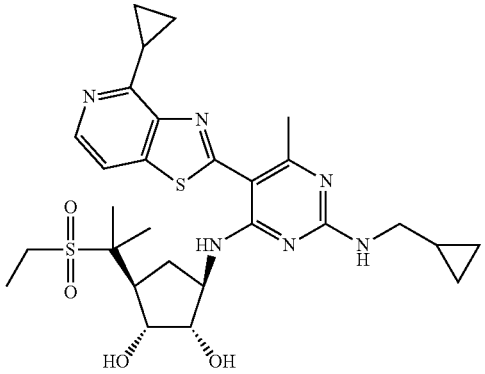
5054	
5058	
5055	
5059	

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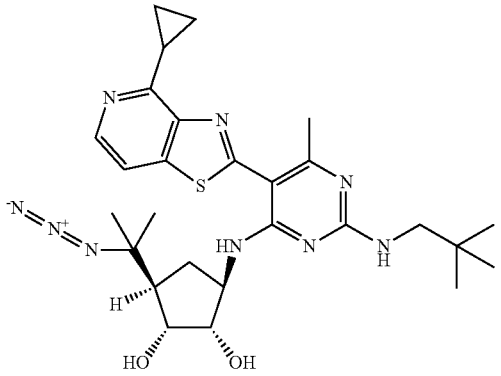
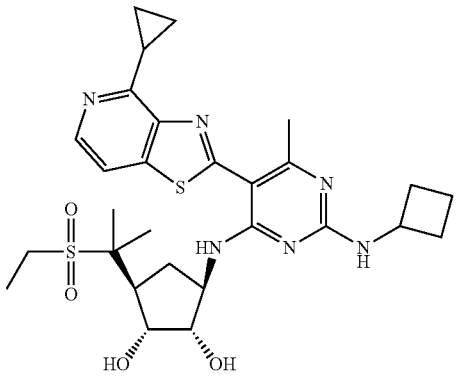
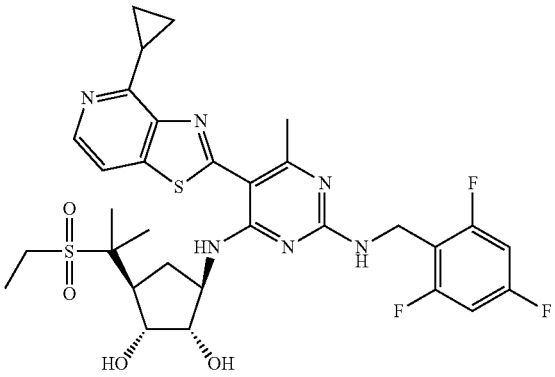
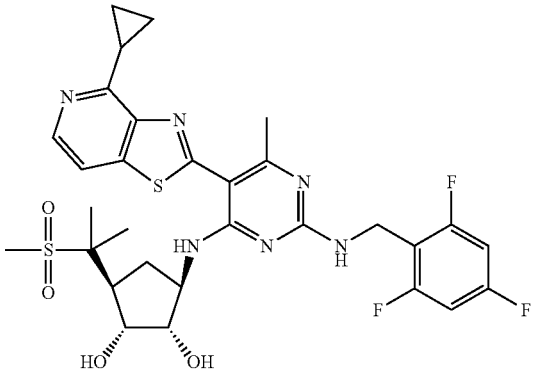
5056	
5060	
5061	
5065	

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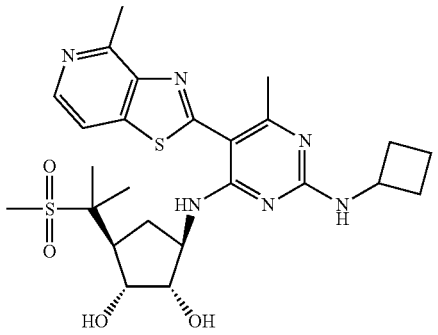
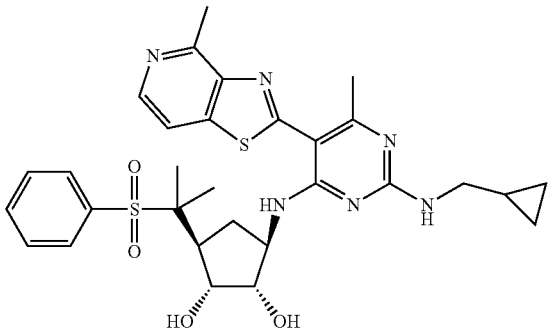
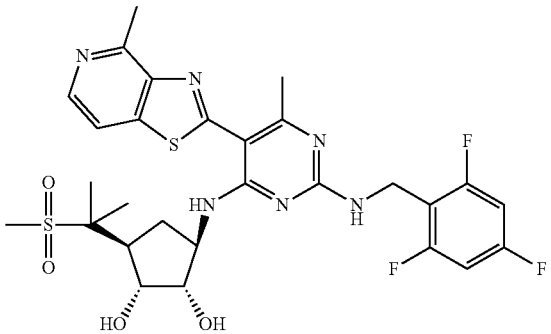
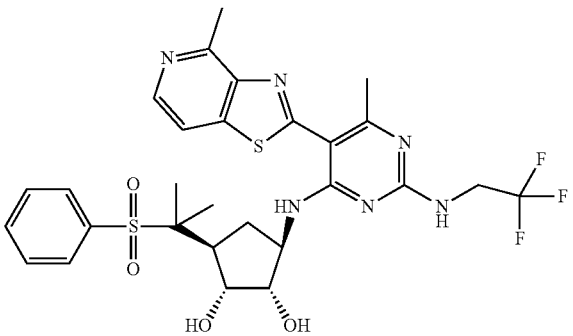
5062	
5066	
5063	
5067	

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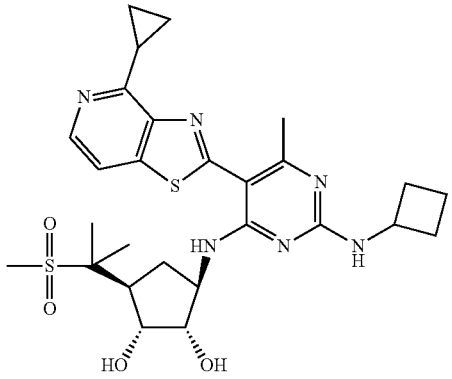
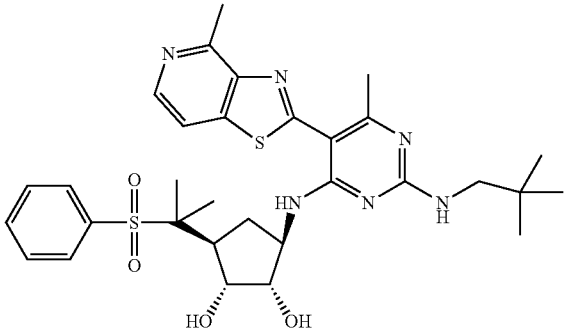
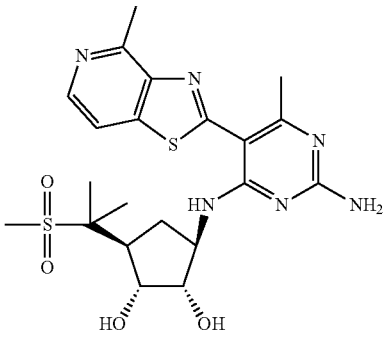
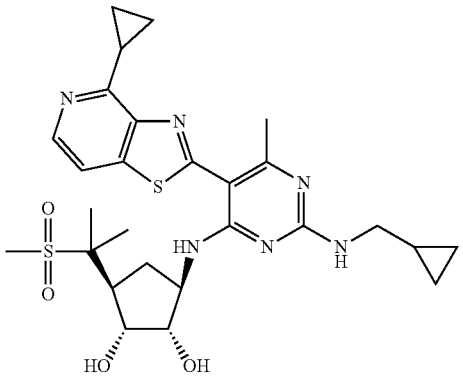
5064	
5068	
5069	
5073	

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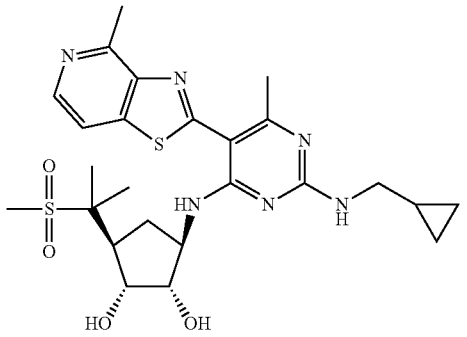
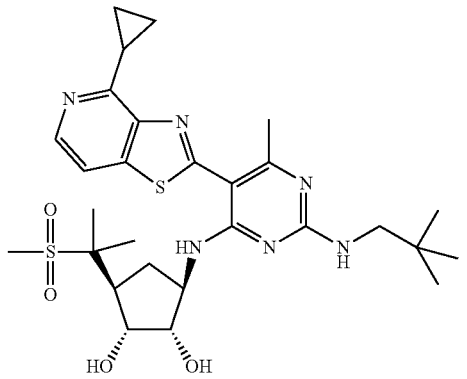
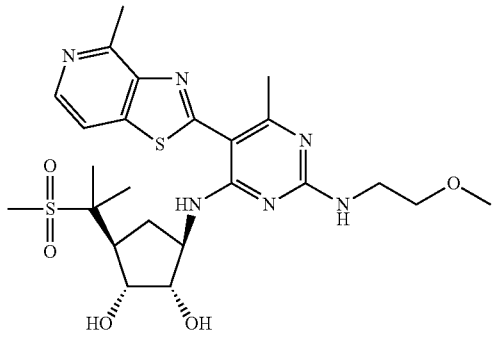
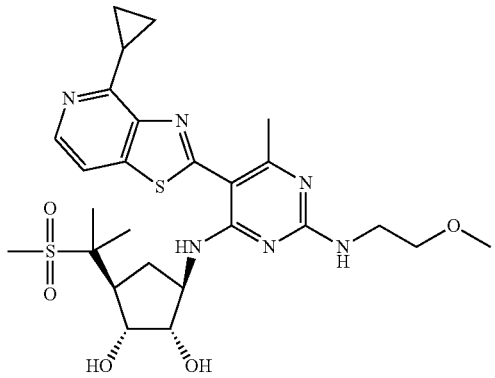
5070	
5074	
5071	
5075	

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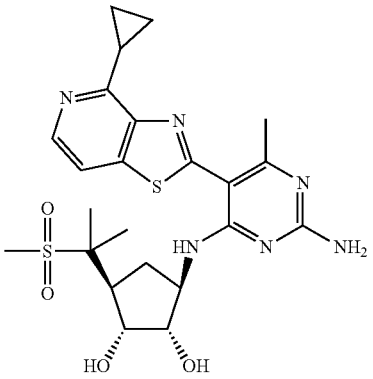
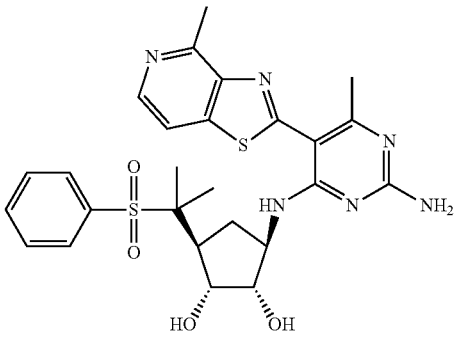
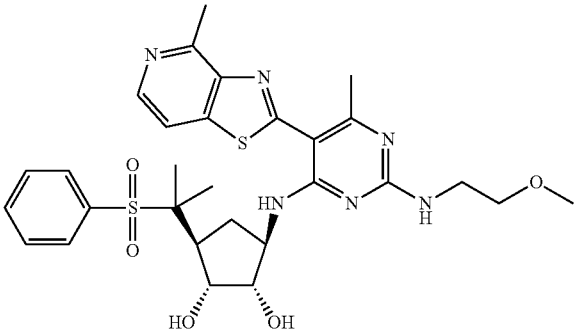
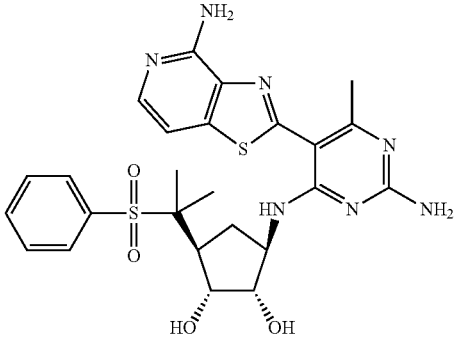
5072	
5076	
5077	
5081	

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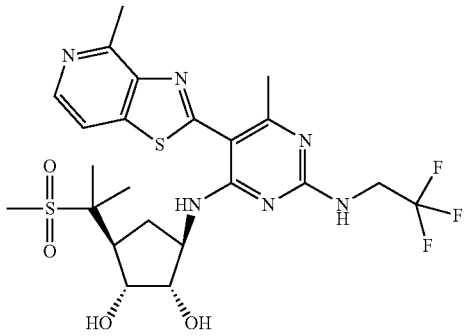
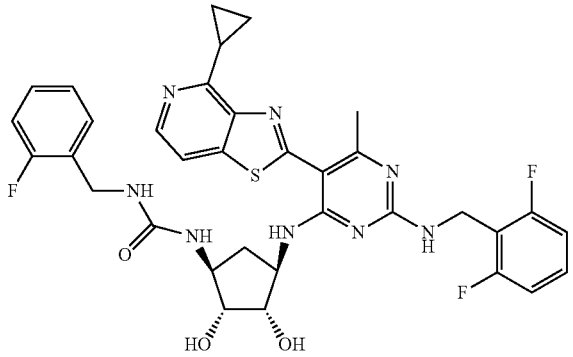
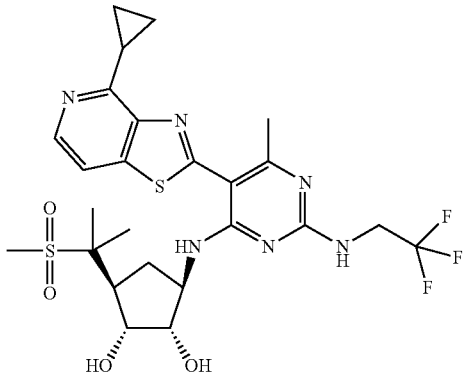
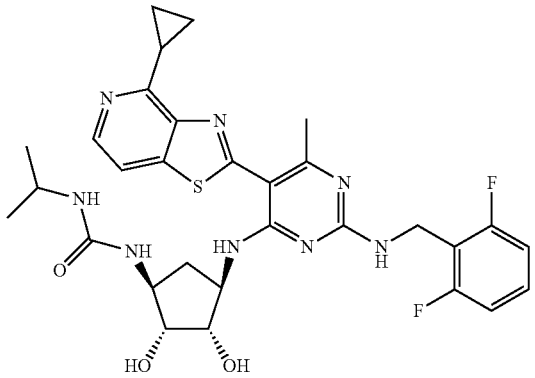
5078	
5082	
5079	
5083	

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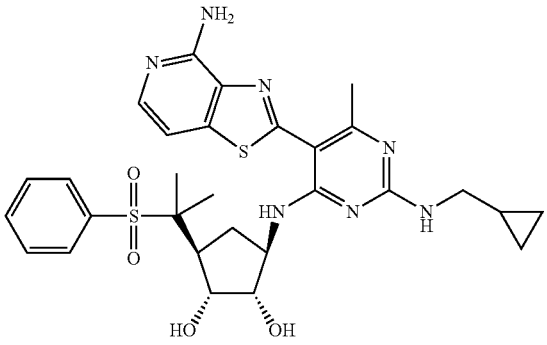
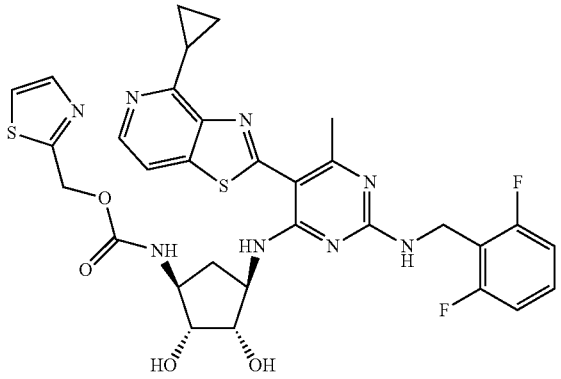
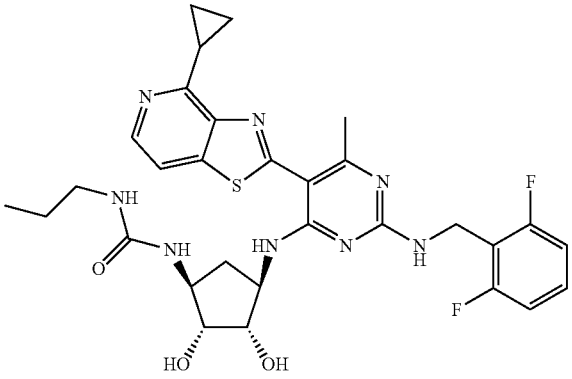
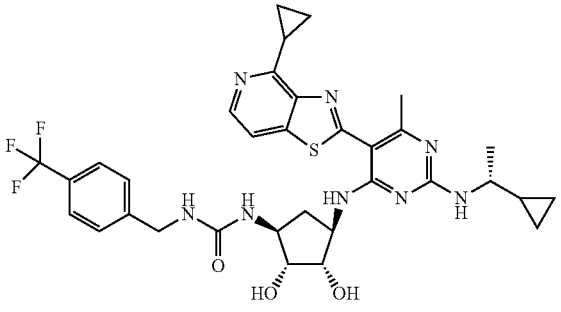
5080	
5084	
5085	
5090	

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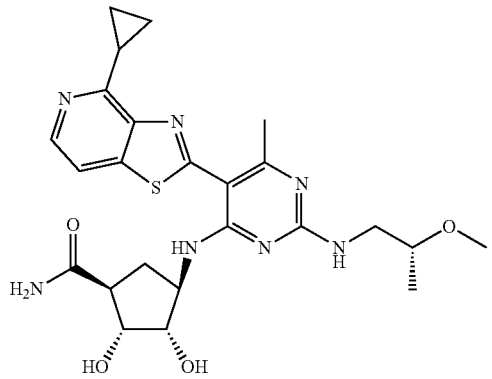
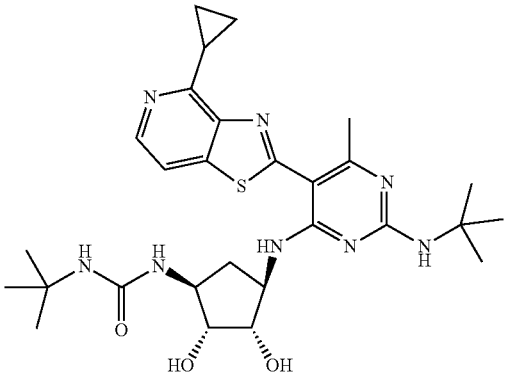
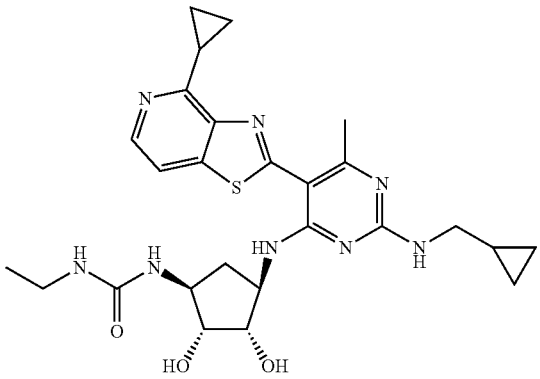
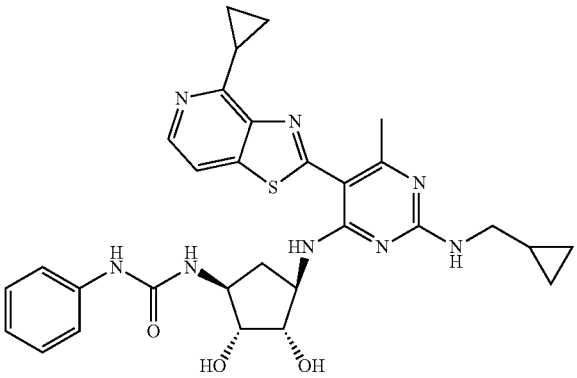
5086	
5091	
5087	
5092	

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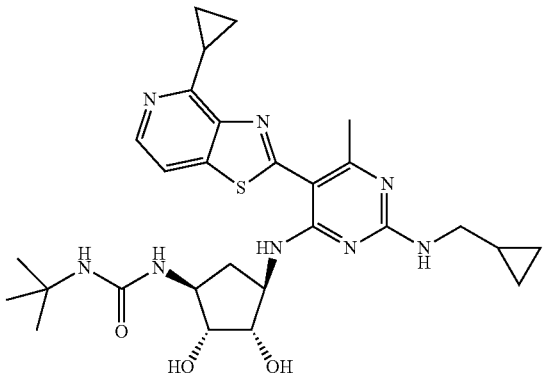
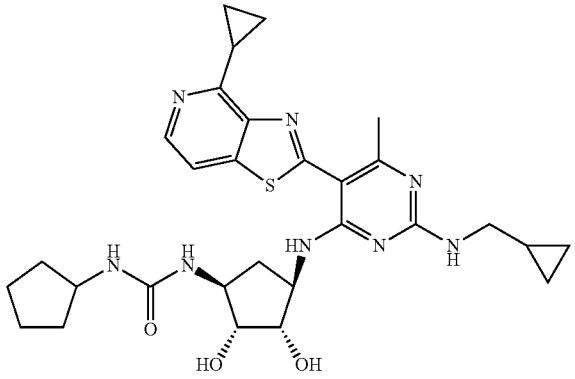
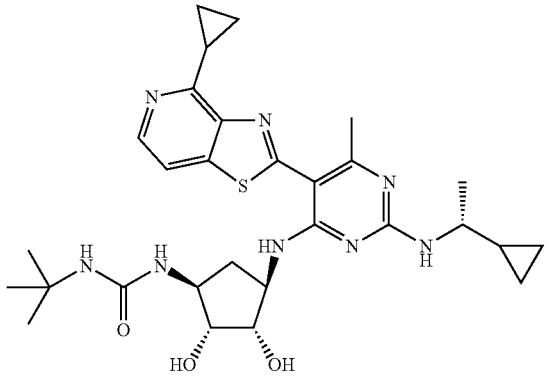
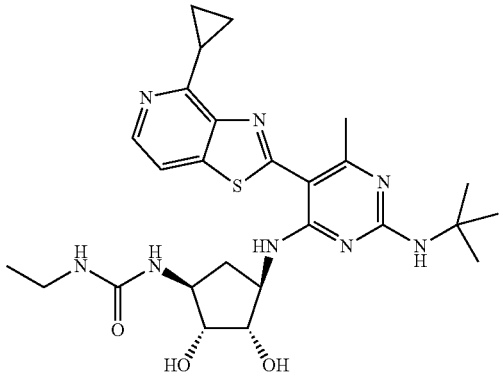
5088	
5093	
5089	
5094	

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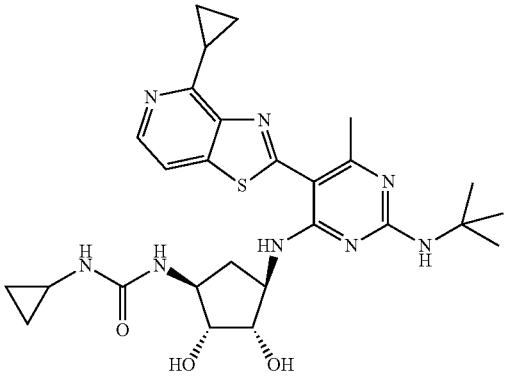
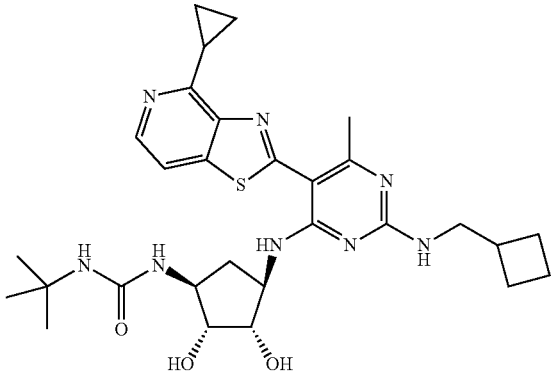
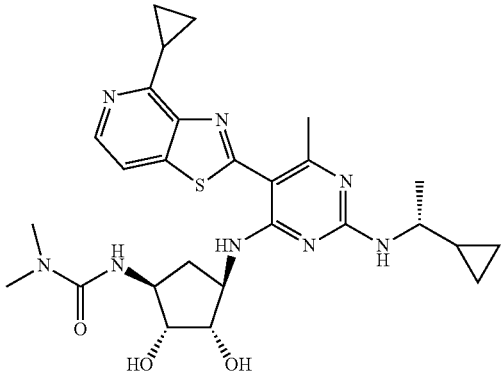
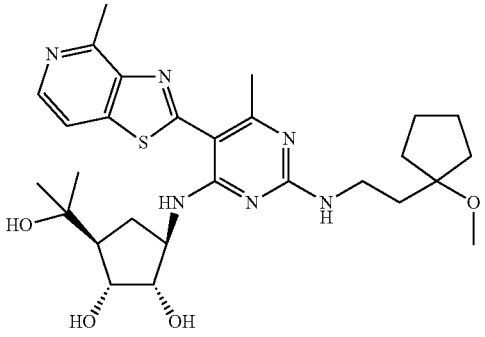
Compd #	Structure
5095	
5100	
5096	
5101	

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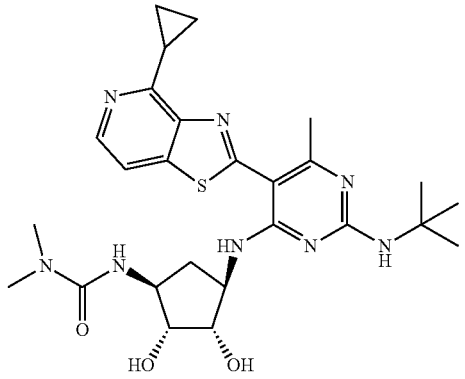
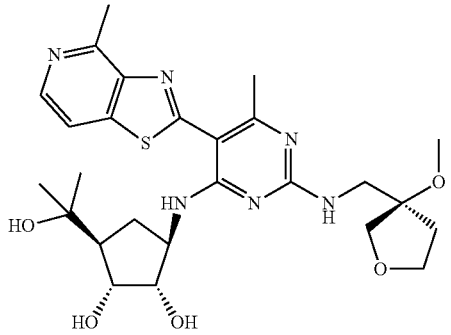
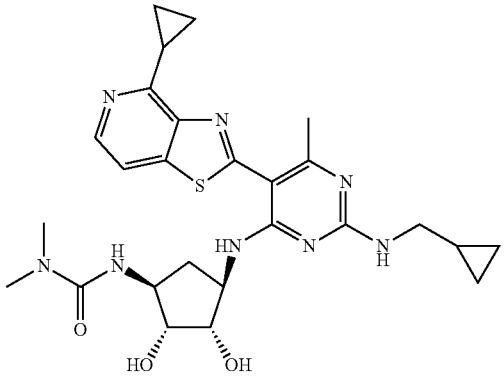
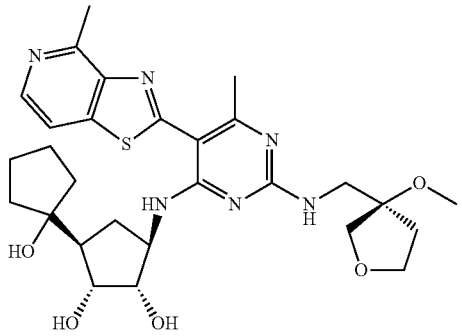
5097	
5102	
5098	
5103	

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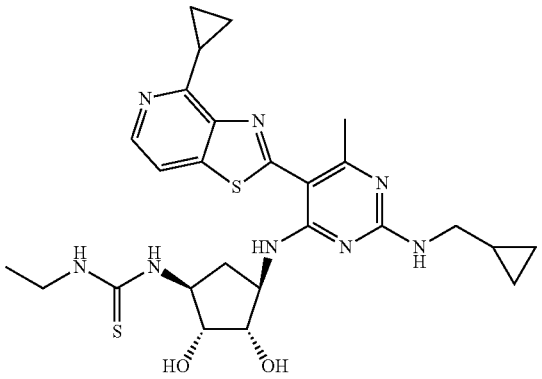
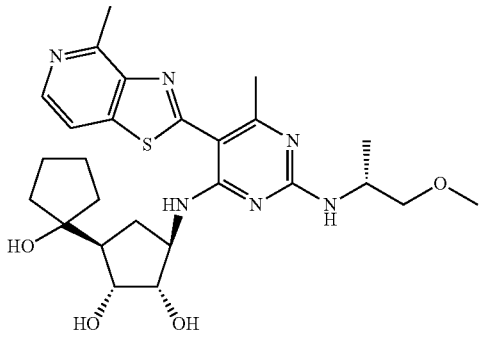
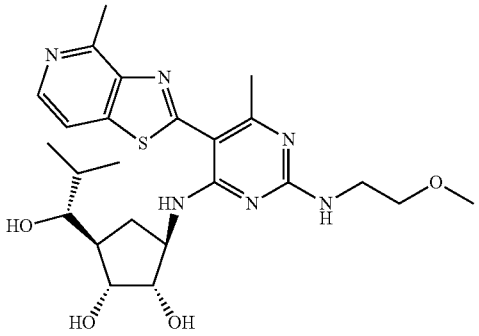
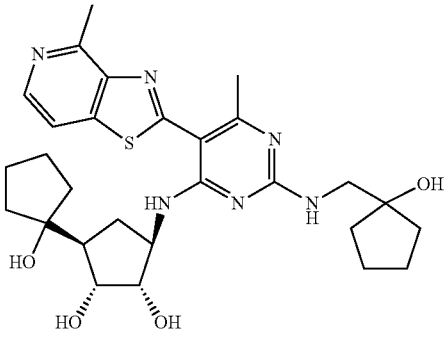
5099	
5104	
5105	
5110	

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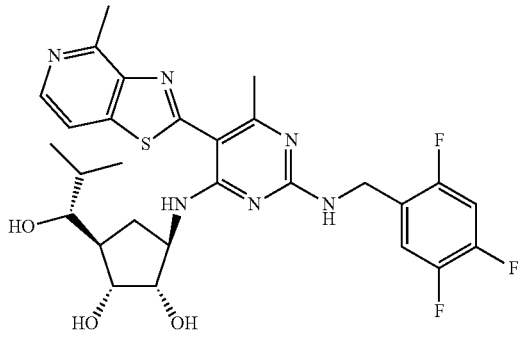
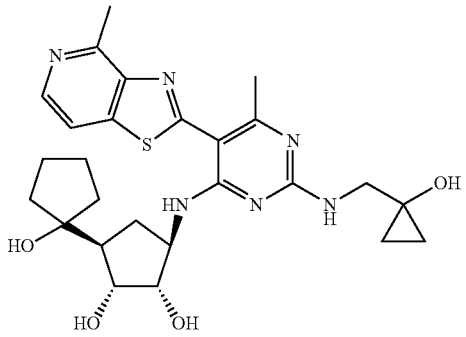
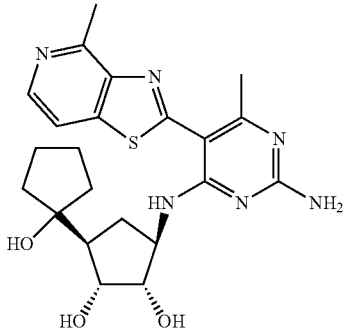
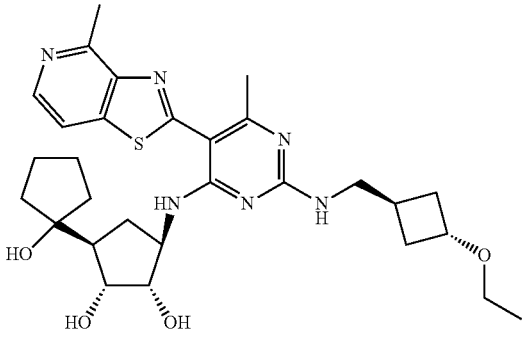
5106	
5111	
5107	
5112	

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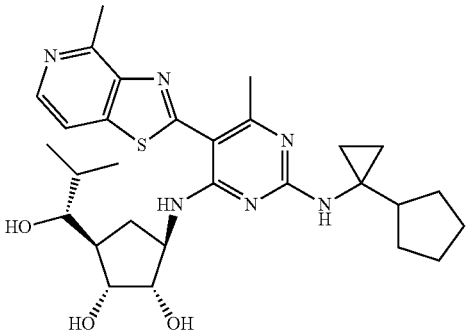
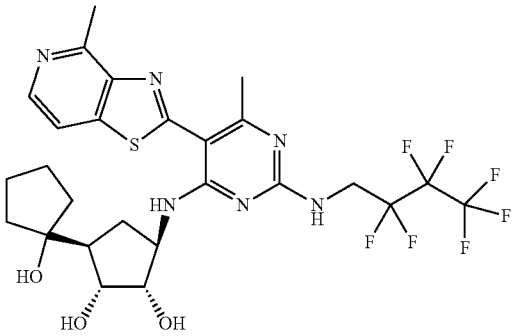
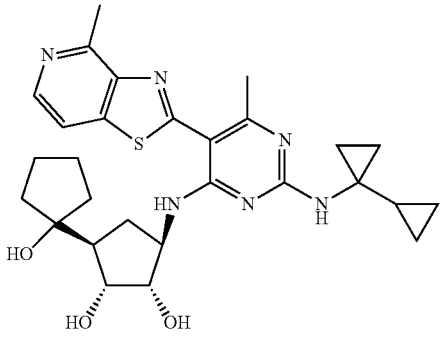
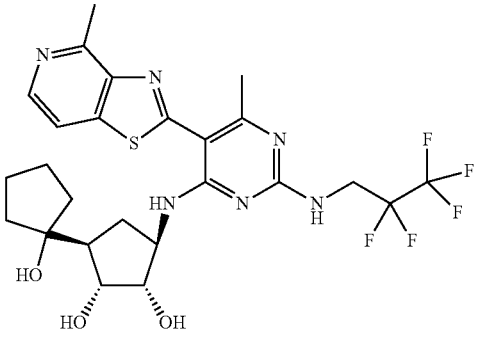
Compd #	Structure
5108	
5113	
5109	
5114	

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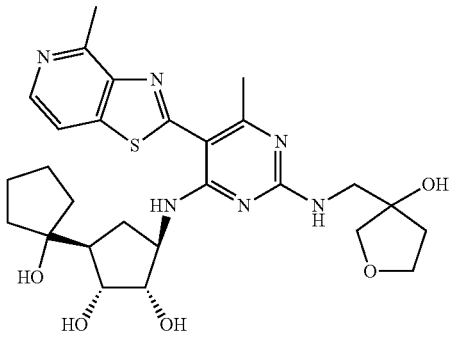
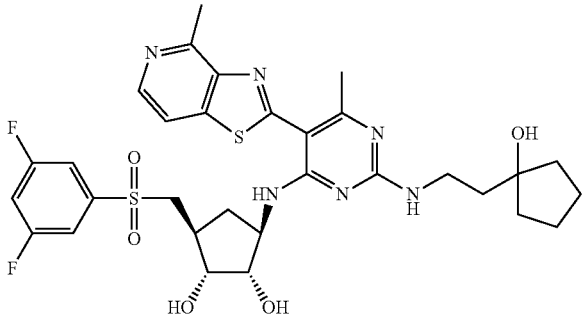
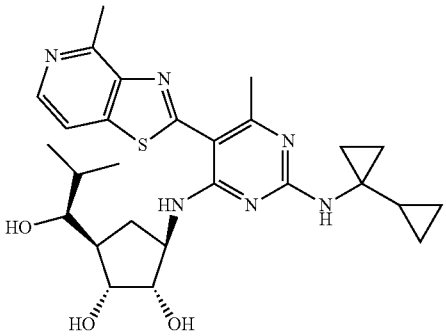
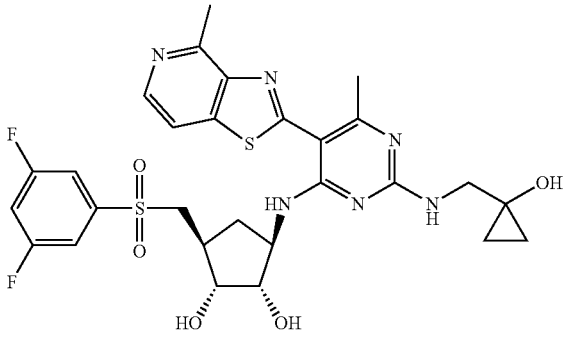
Compd #	Structure
5115	
5120	
5122	
5118	

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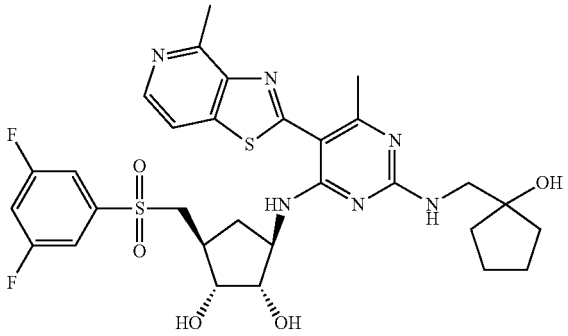
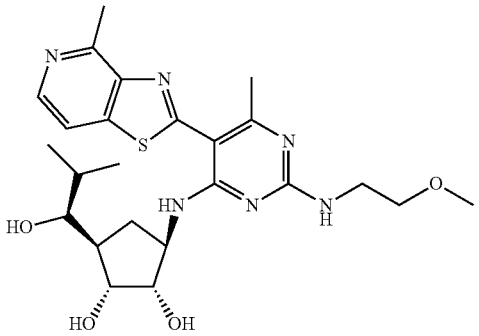
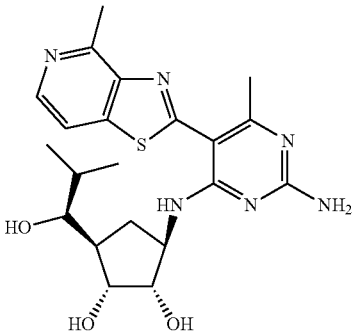
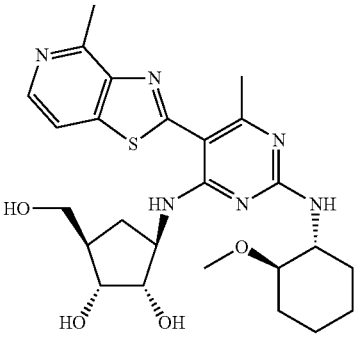
5119	
5123	
5125	
5139	

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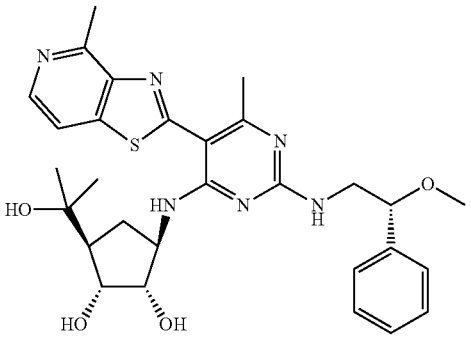
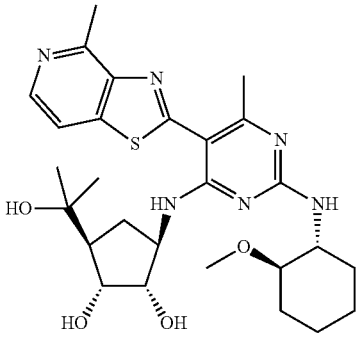
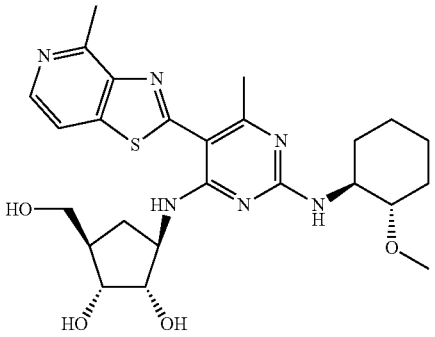
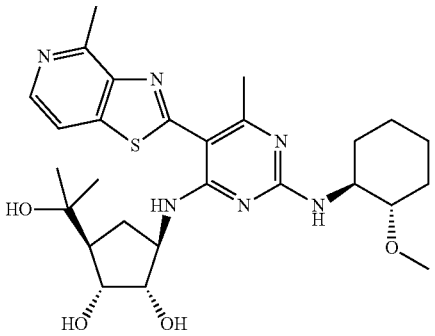
5135	
5140	
5136	
5137	

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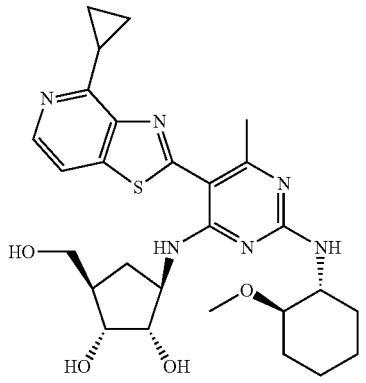
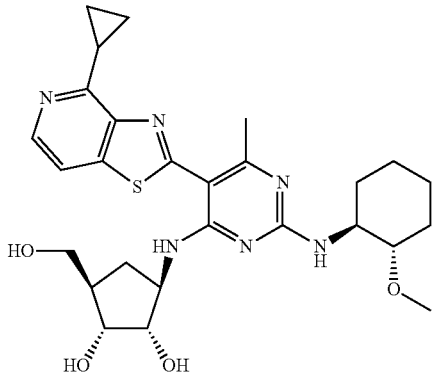
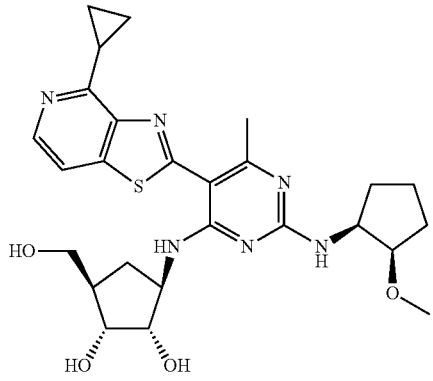
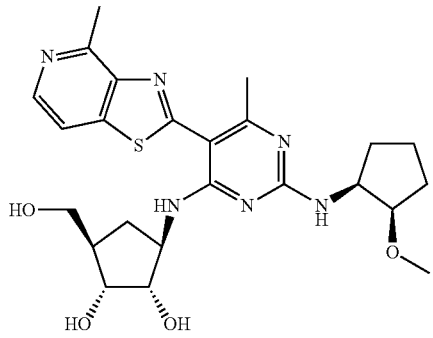
5141	
5138	
5142	
5143	

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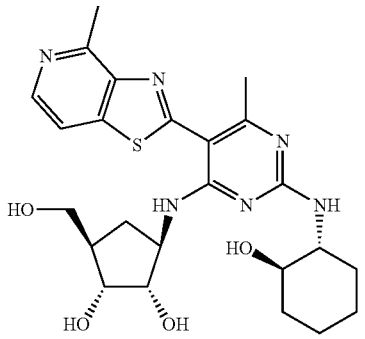
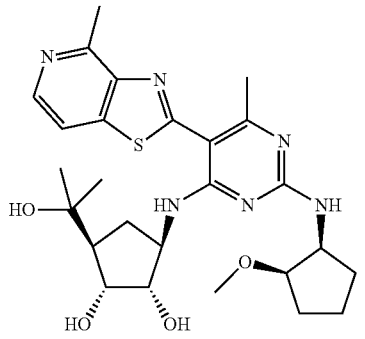
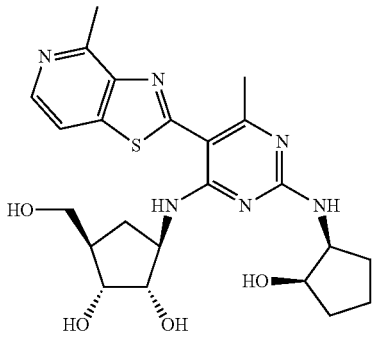
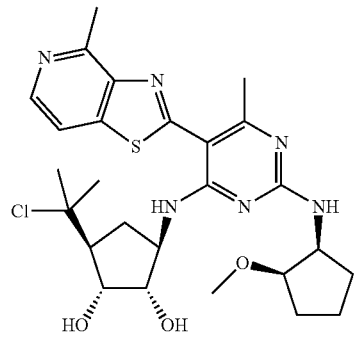
5148	
5144	
5149	
5145	

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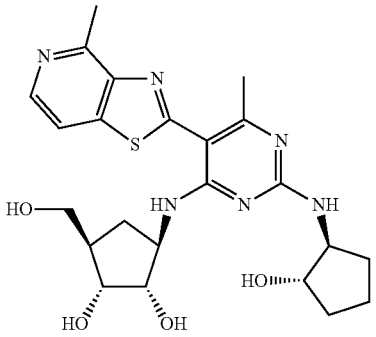
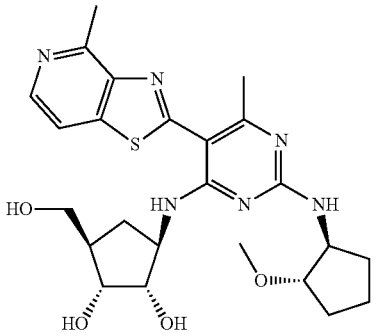
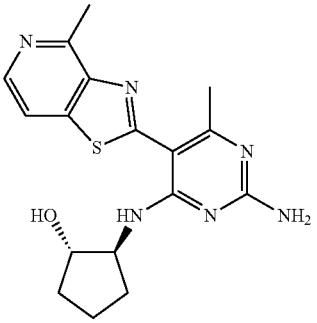
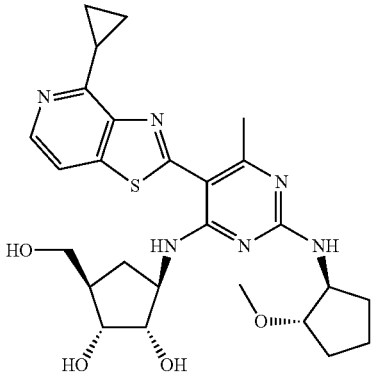
5150	
5146	
5151	
5147	

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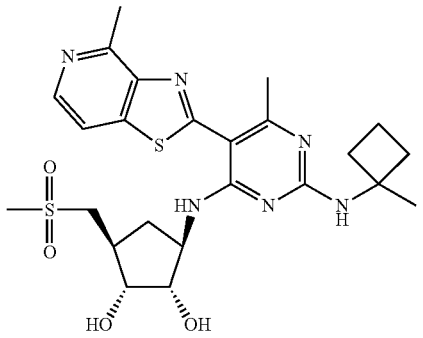
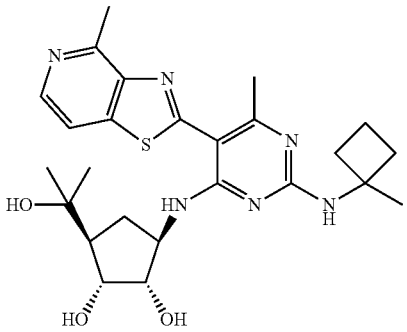
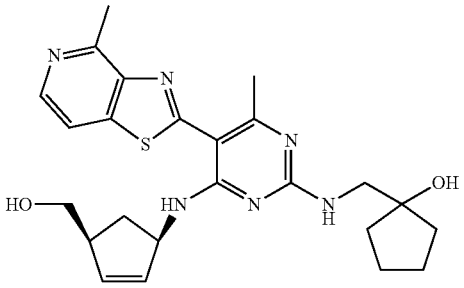
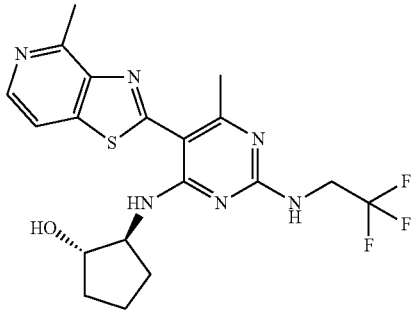
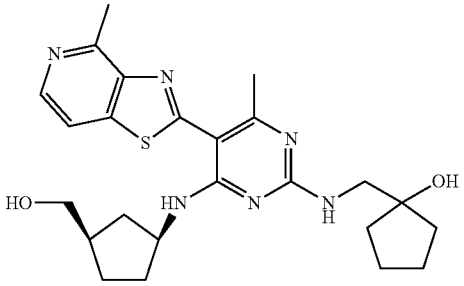
Compd #	Structure
5152	
5153	
5158	
5154	
5159	

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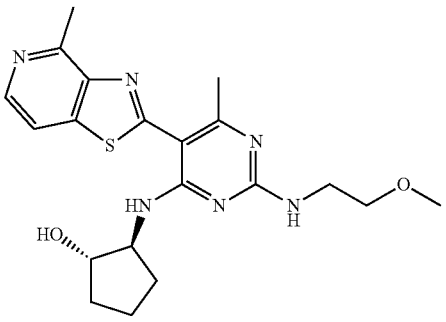
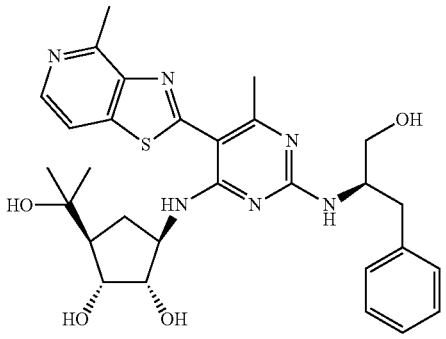
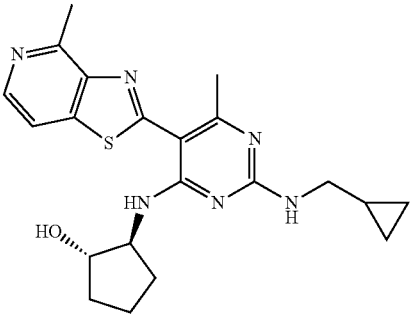
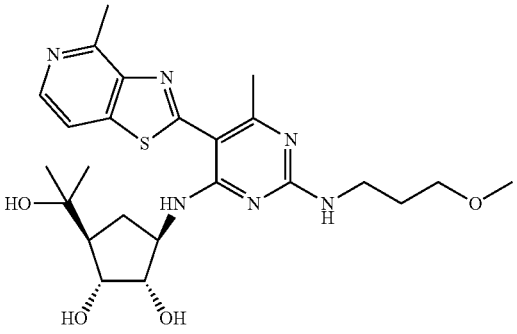
5155	
5160	
5156	
5161	

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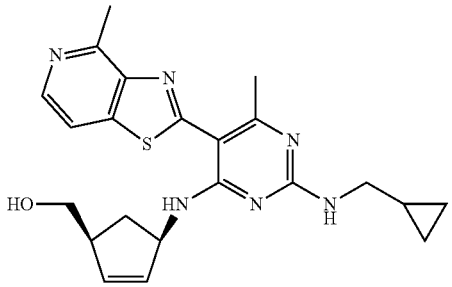
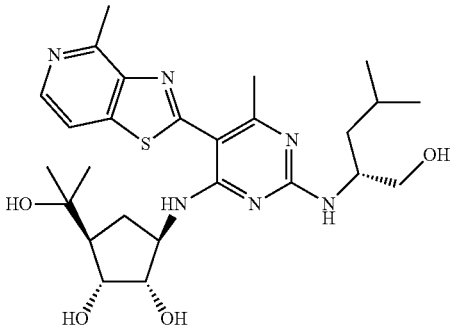
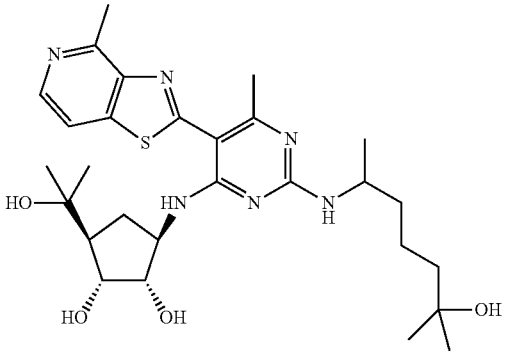
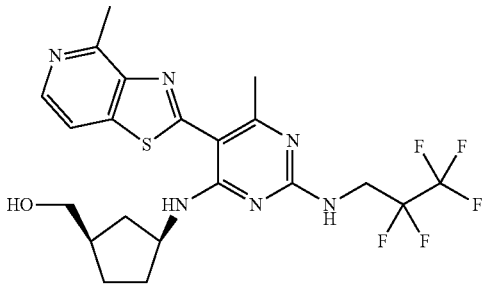
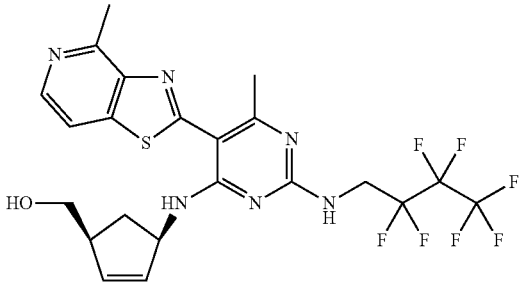
Compd #	Structure
5157	
5162	
5163	
5168	
5164	

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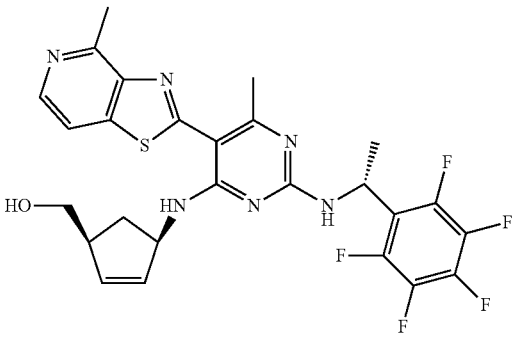
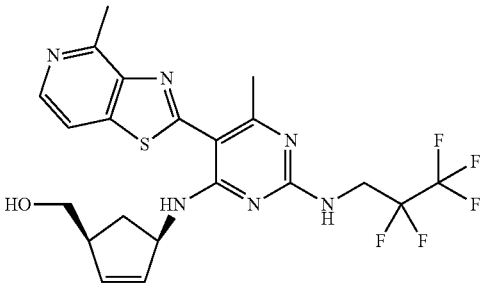
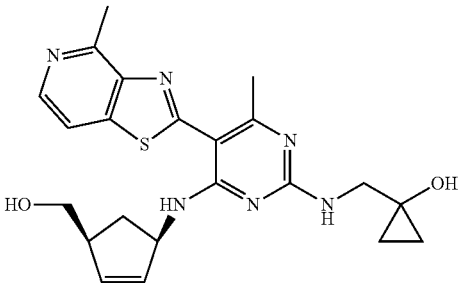
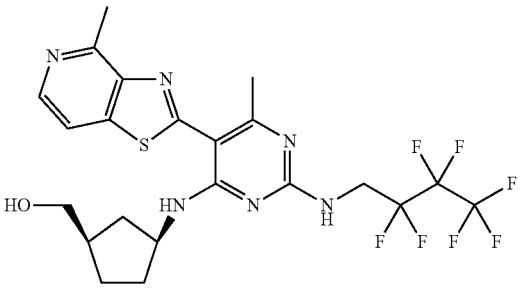
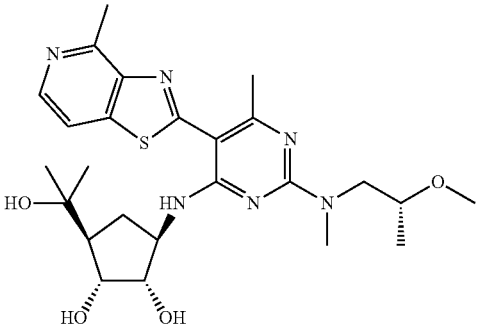
5169	
5165	
5170	
5166	
5171	

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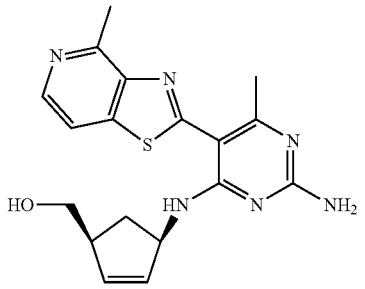
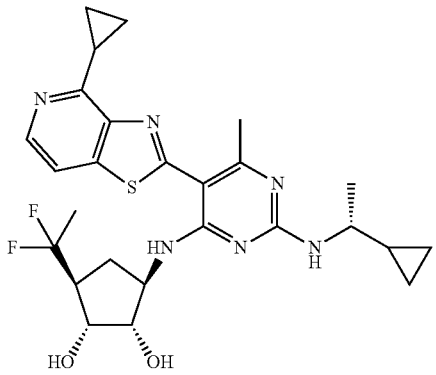
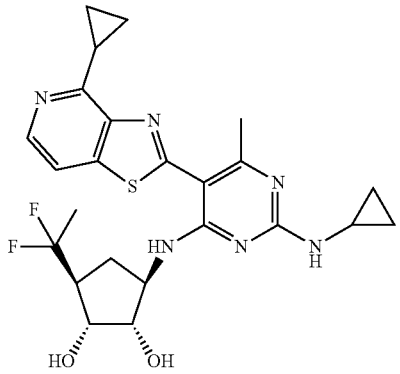
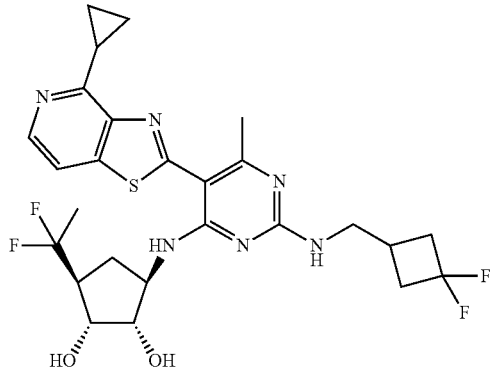
5167	
5172	
5173	
5177	

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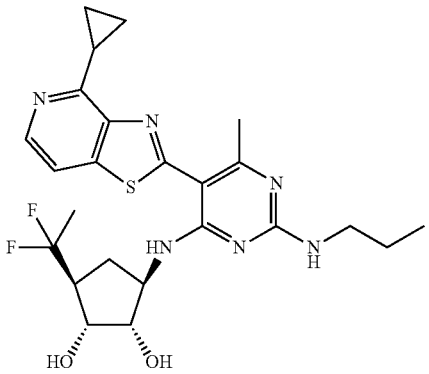
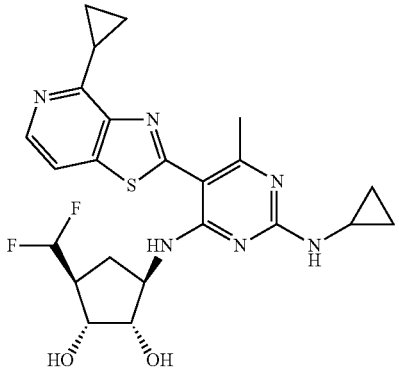
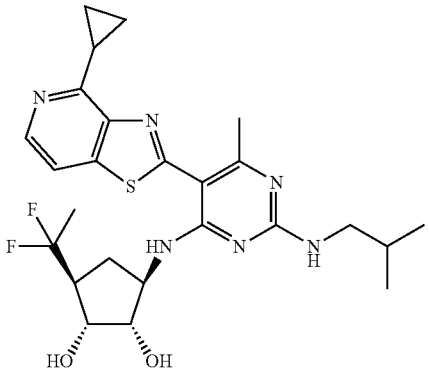
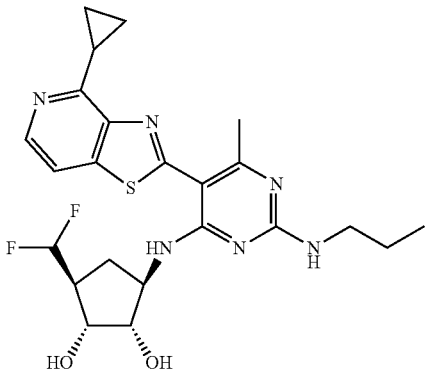
5174	
5178	
5175	
5179	

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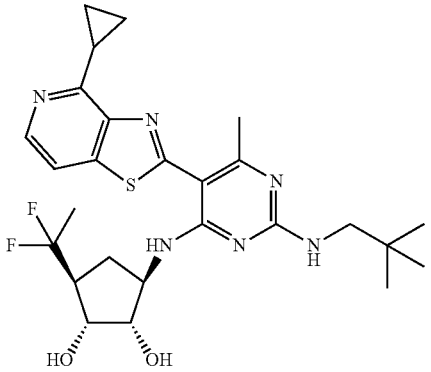
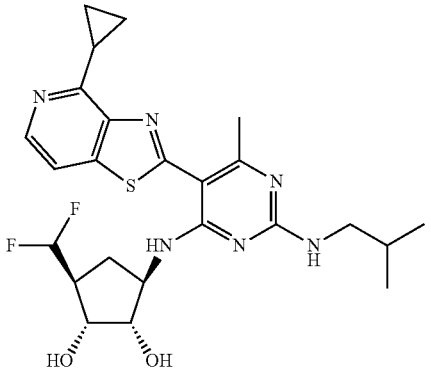
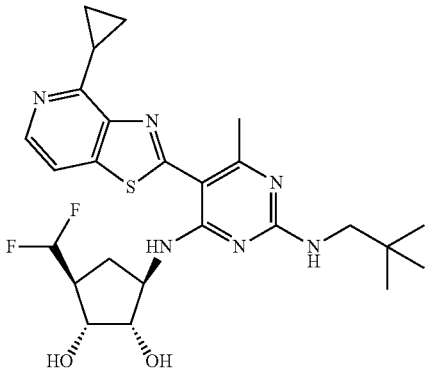
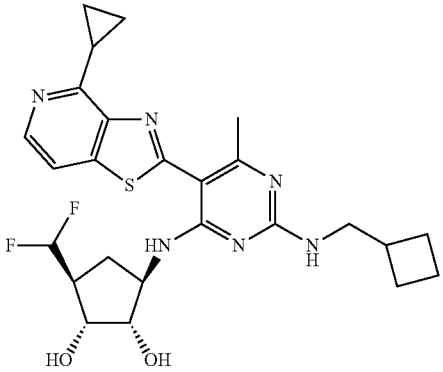
5176	
5180	
5181	
5185	

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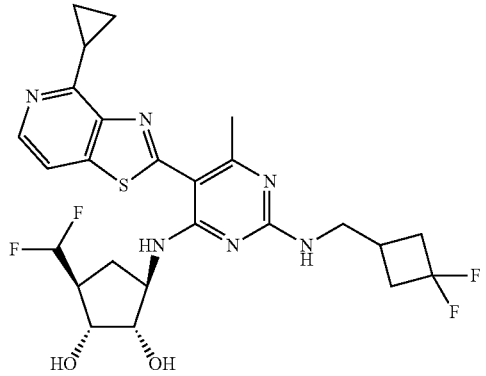
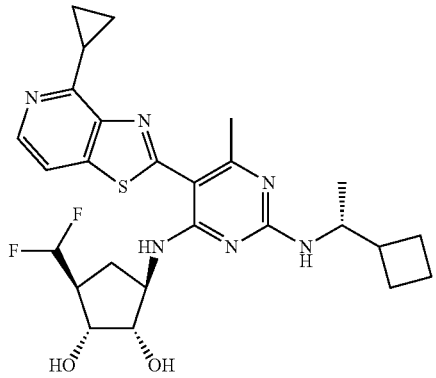
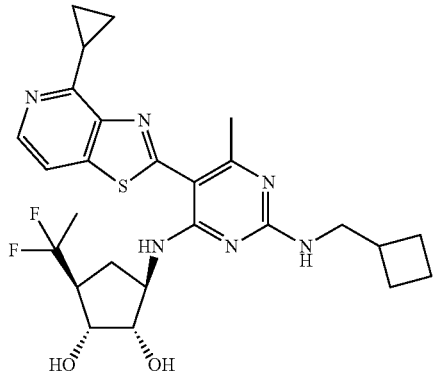
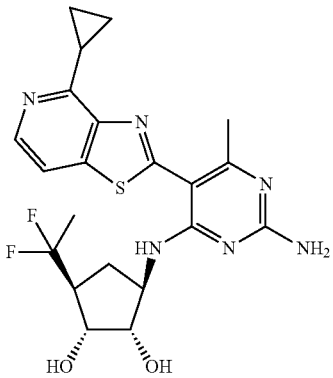
5182	
5186	
5183	
5188	

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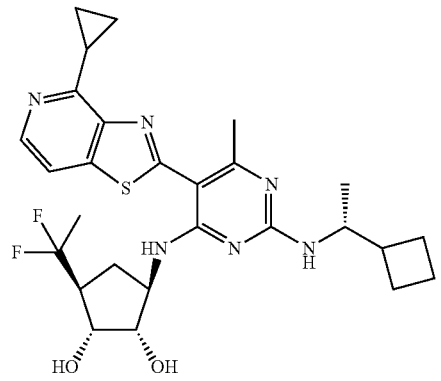
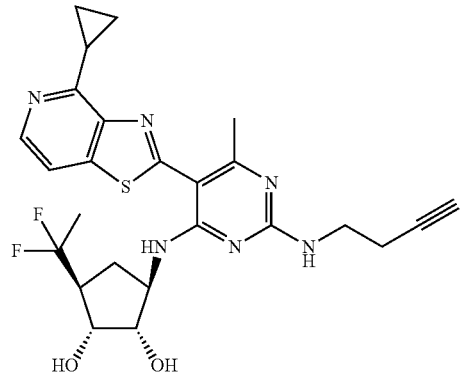
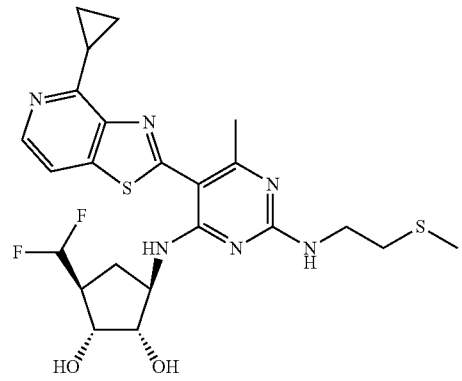
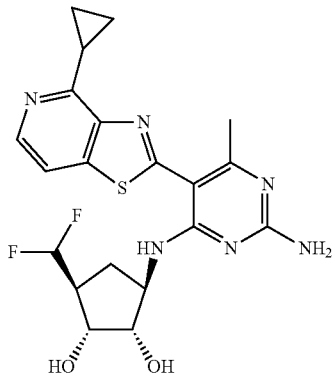
5184	
5189	
5194	
5190	

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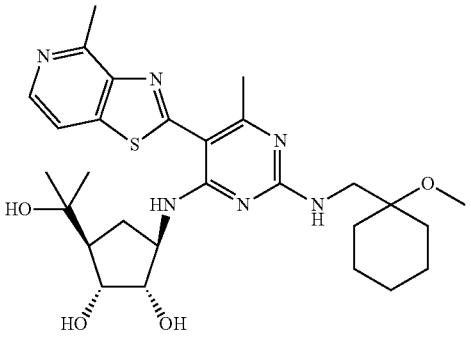
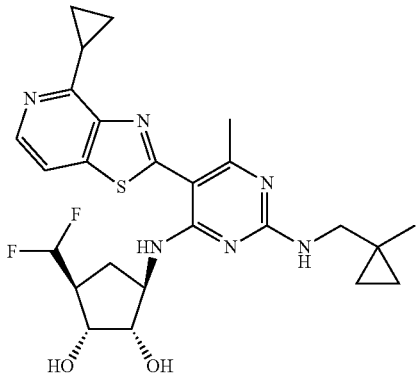
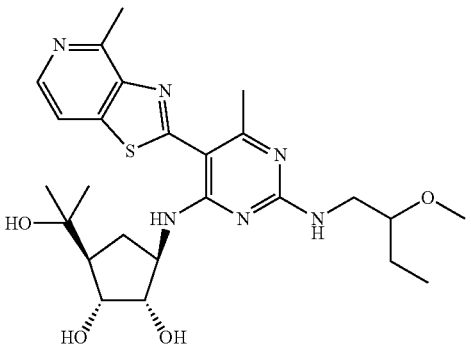
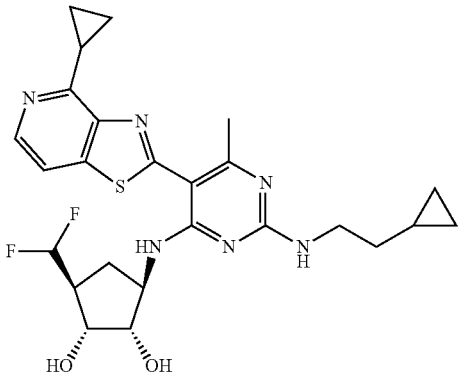
5195	
5191	
5196	
5192	

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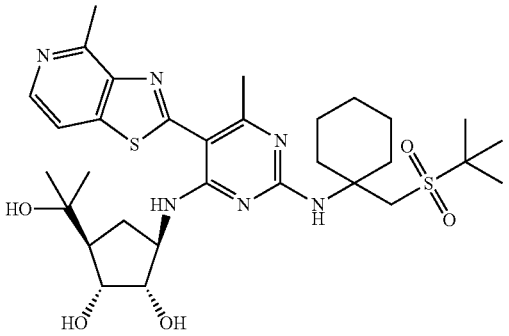
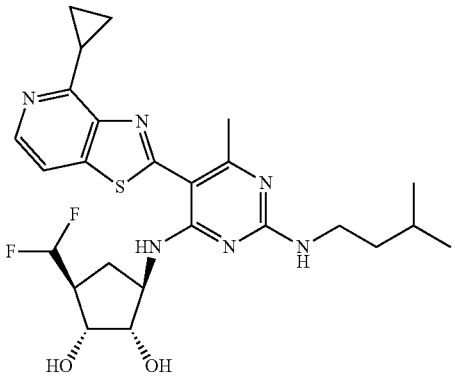
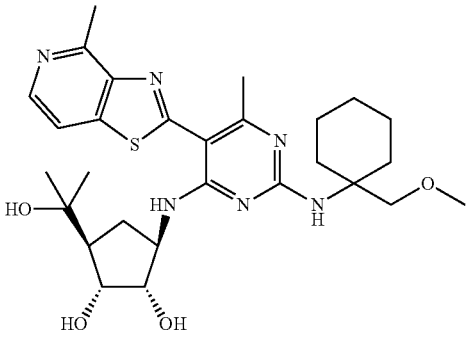
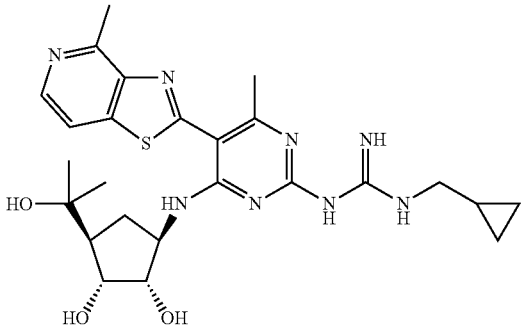
5197	
5193	
5198	
5202	

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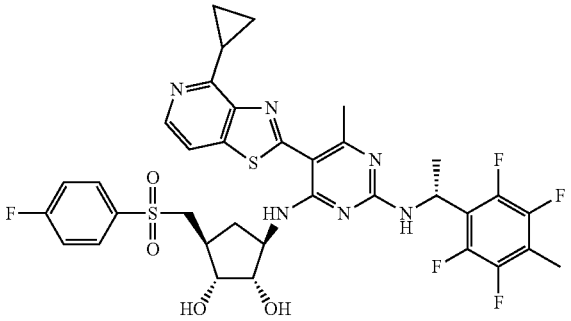
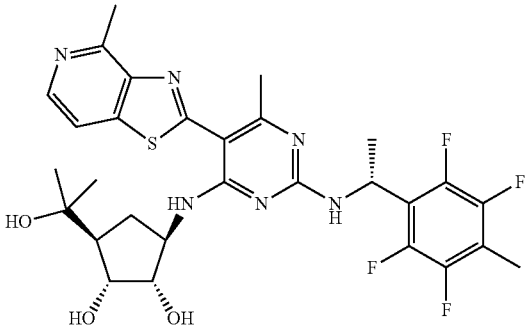
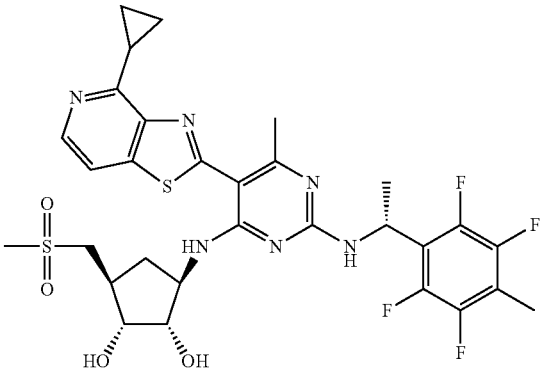
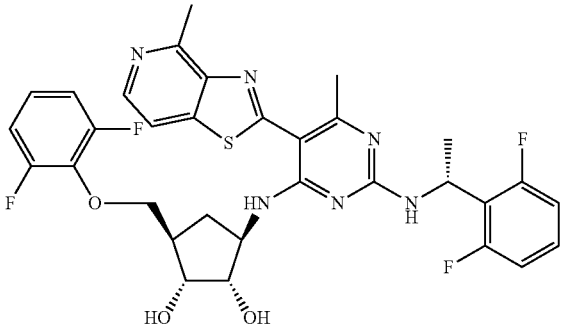
Compd #	Structure
5203	
5204	
5205	
5206	

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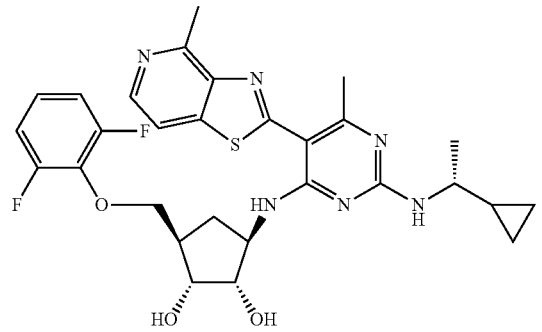
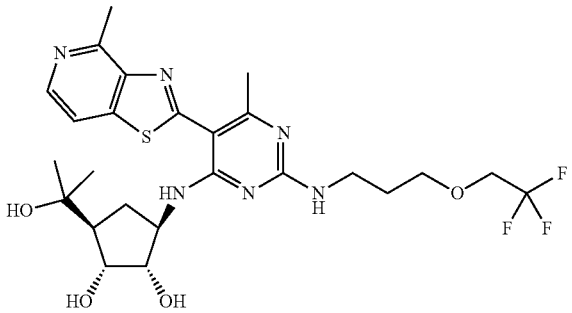
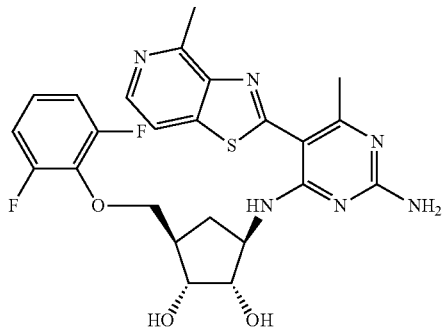
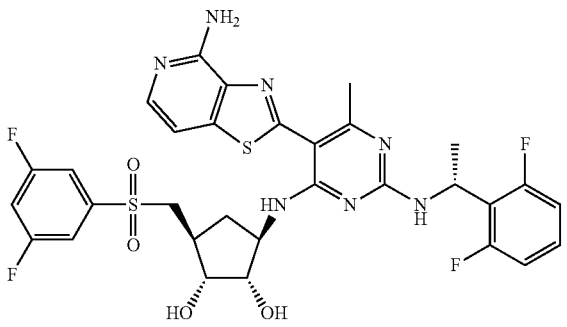
Compd #	Structure
5207	
5208	
5212	
5209	

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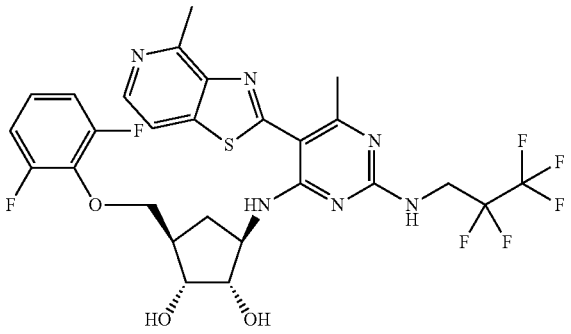
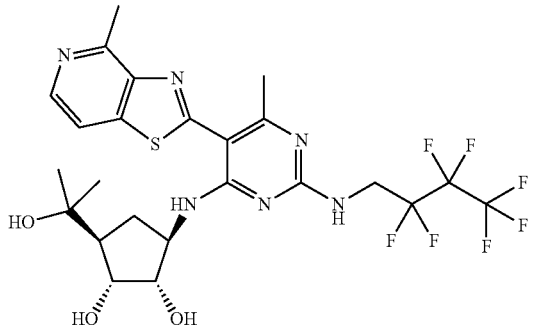
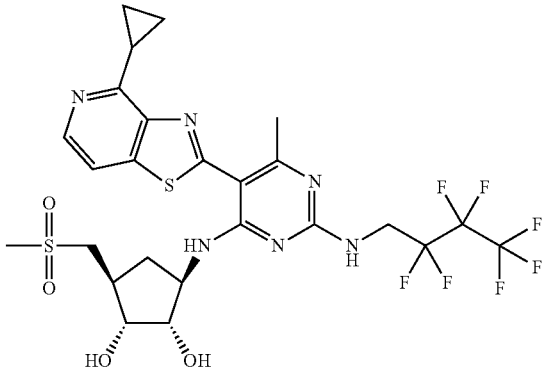
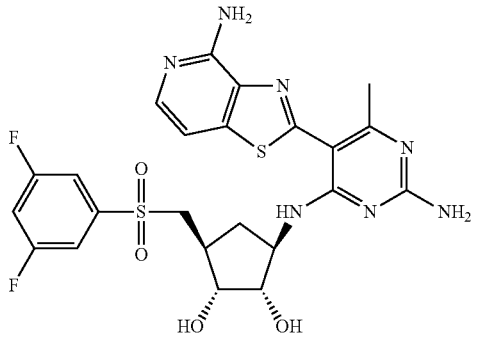
5213	
5210	
5217	
5211	

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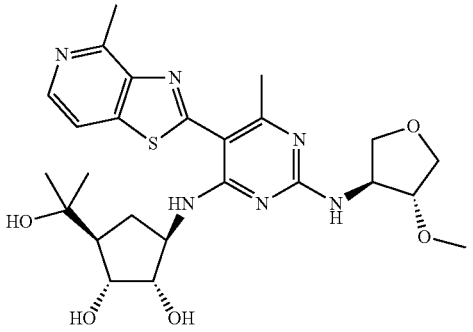
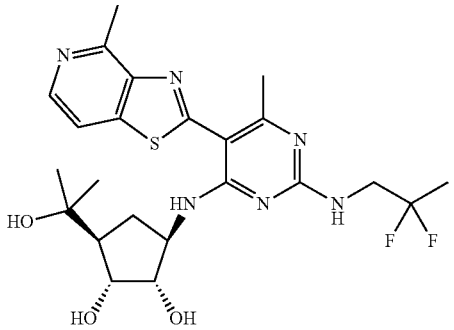
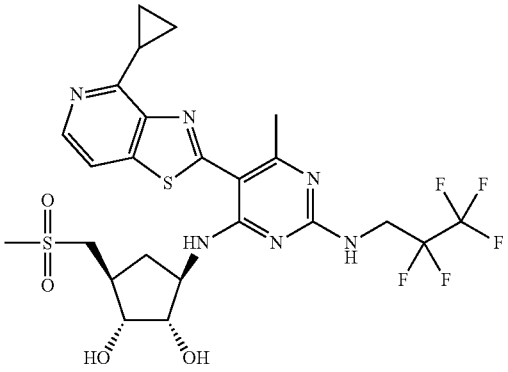
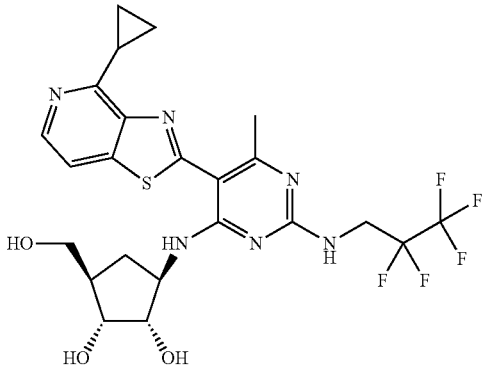
5218	
5221	
5223	
5224	

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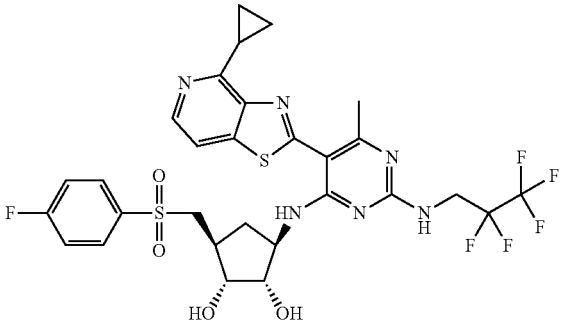
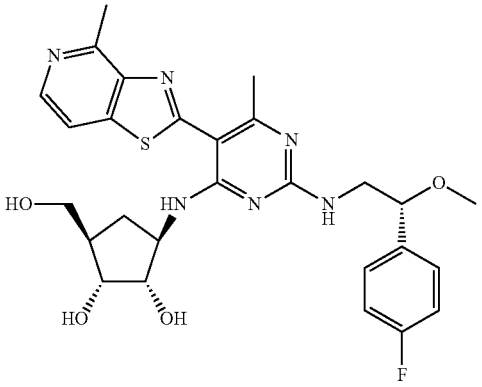
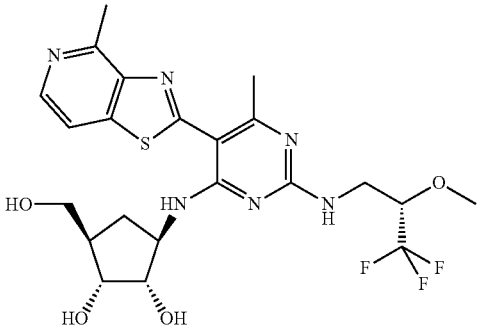
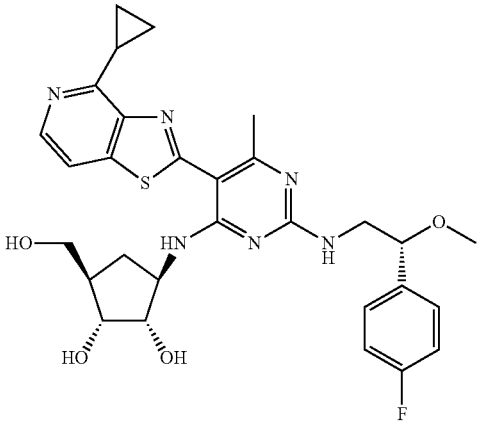
5225	
5226	
5230	
5227	

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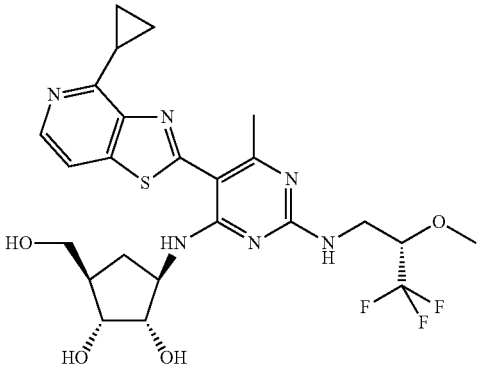
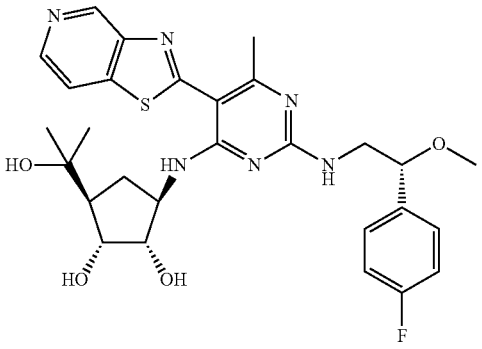
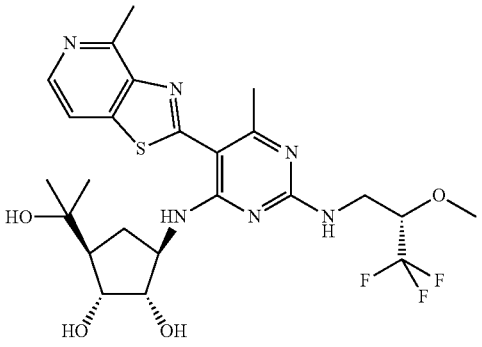
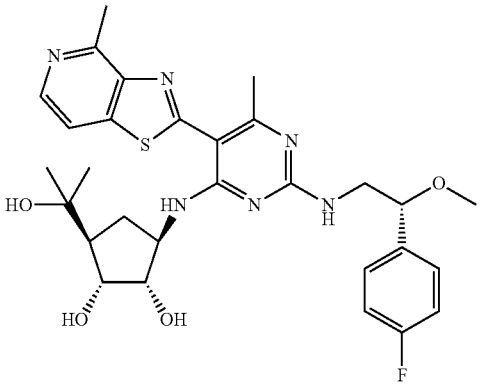
5231	
5228	
5232	
5229	

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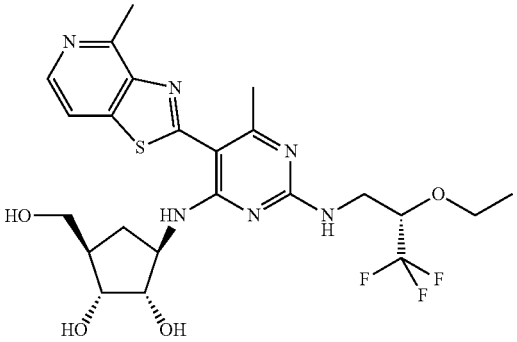
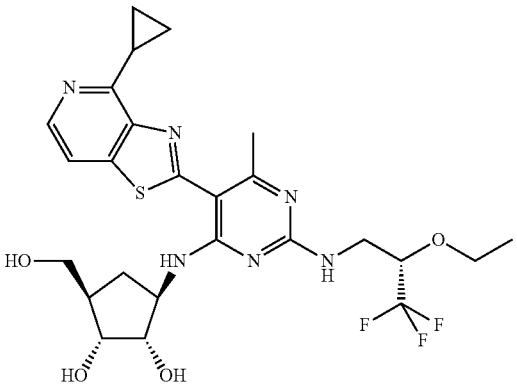
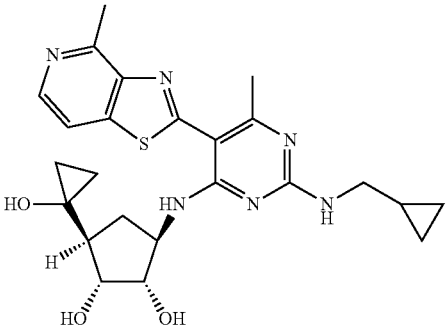
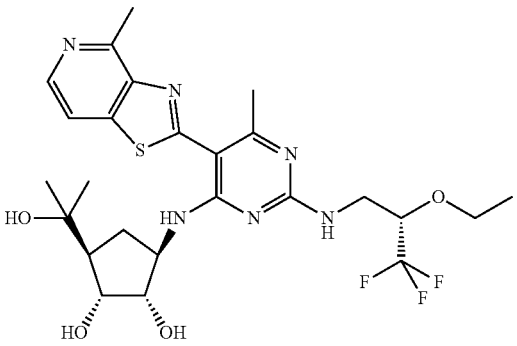
5233	
5234	
5239	
5235	

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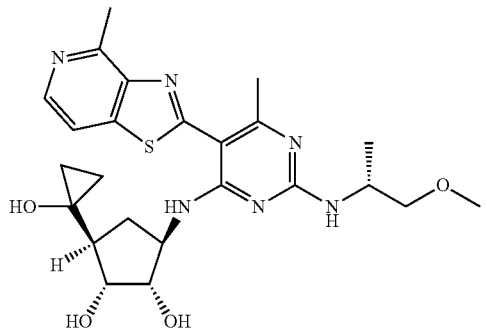
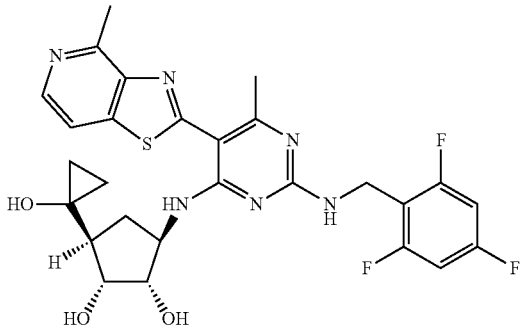
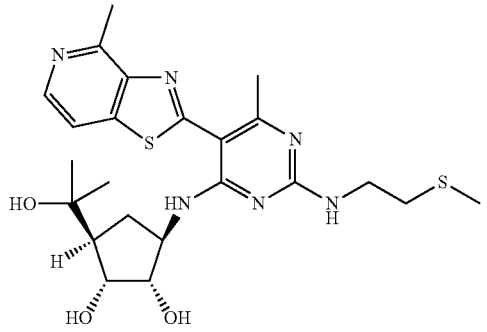
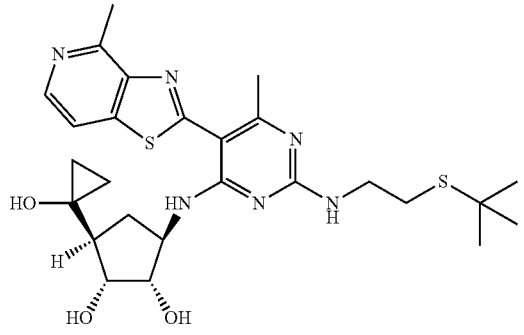
5240	
5236	
5241	
5237	

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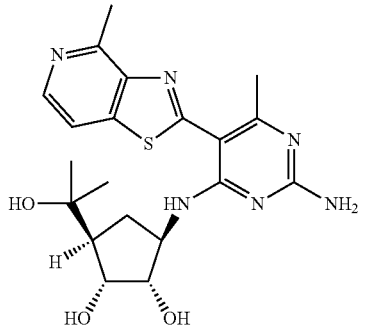
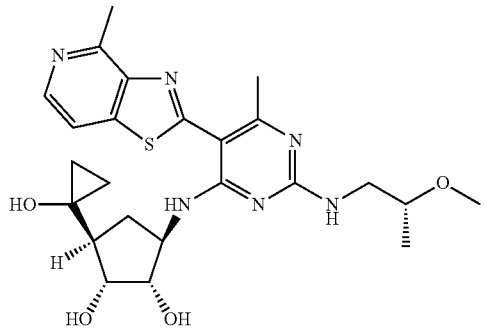
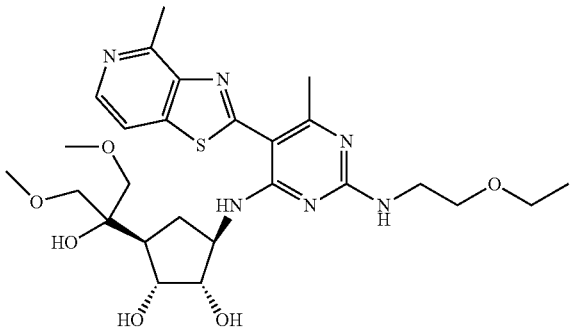
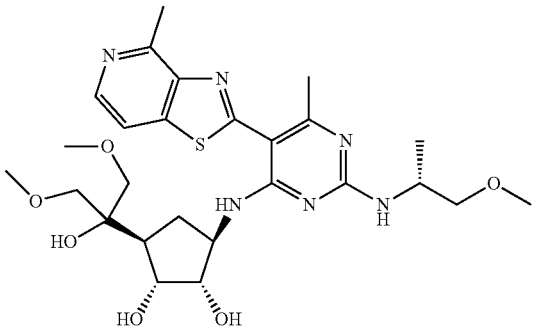
5242	
5238	
5243	
5244	

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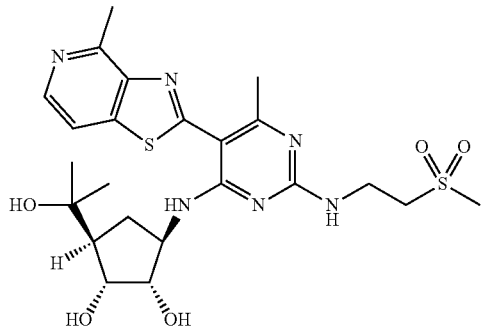
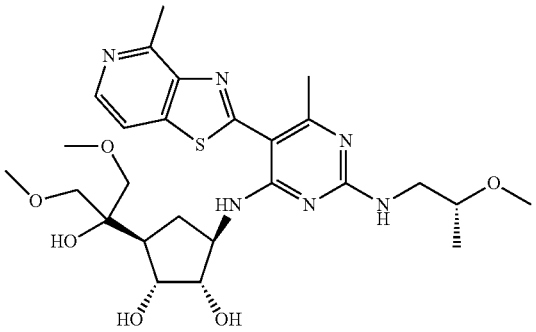
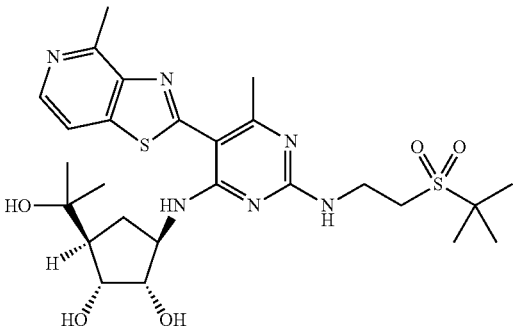
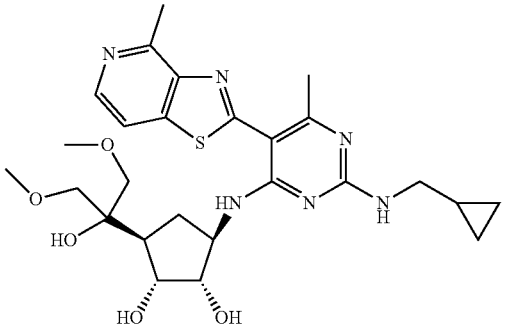
5249	
5245	
5250	
5246	

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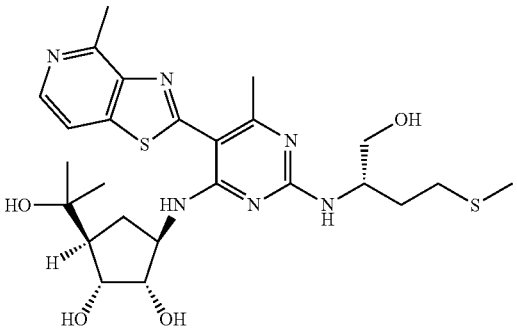
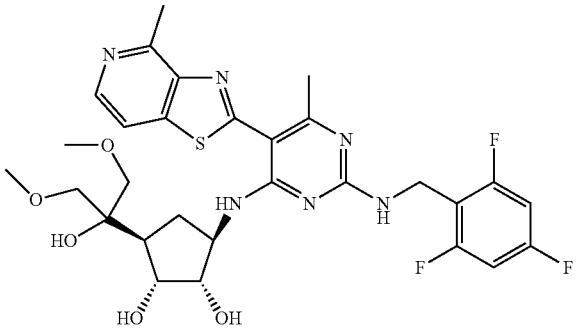
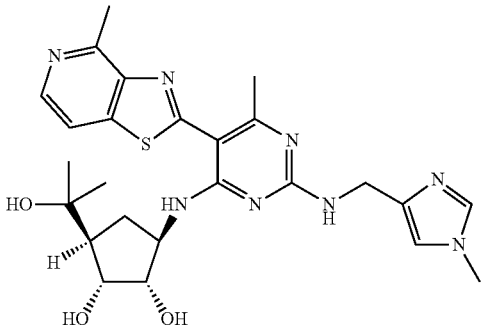
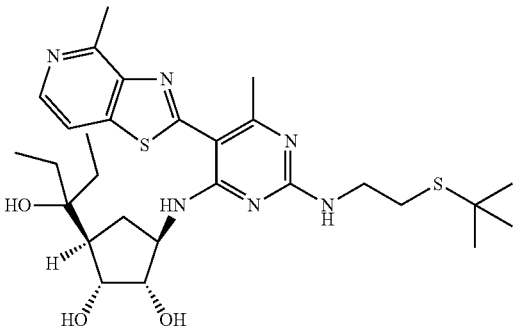
5251	
5247	
5252	
5248	

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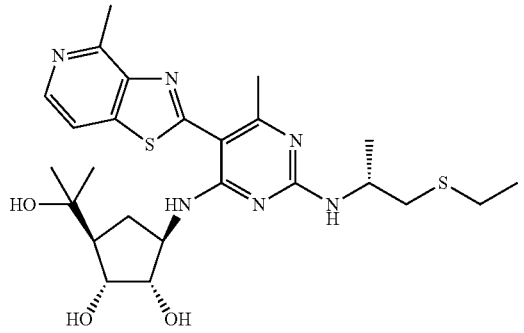
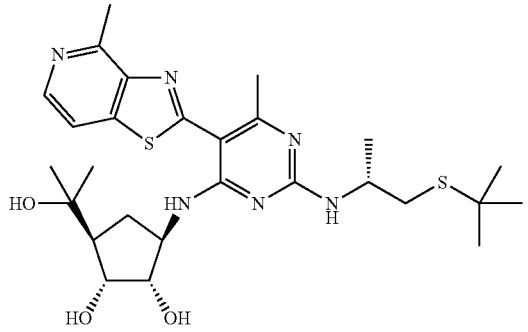
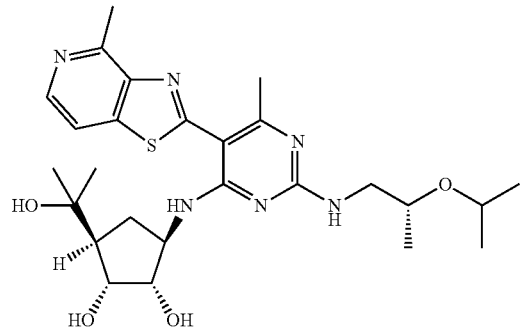
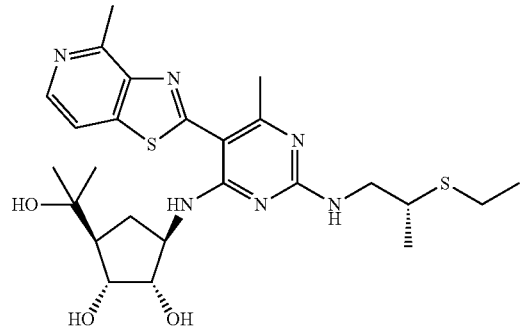
5253	
5254	
5259	
5255	

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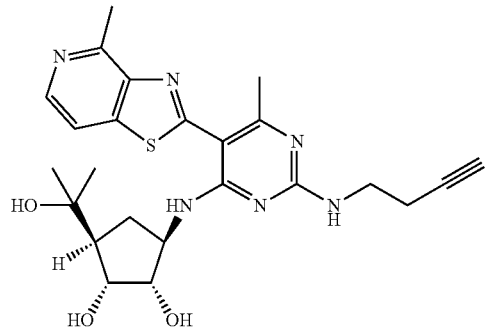
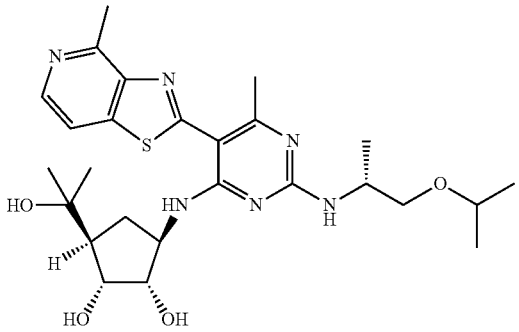
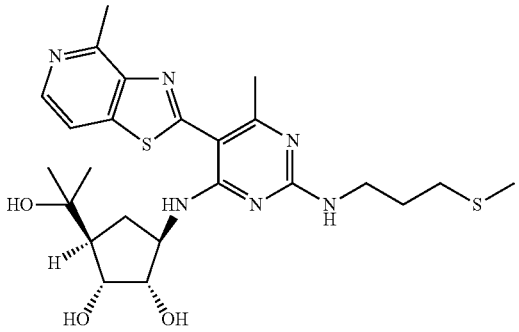
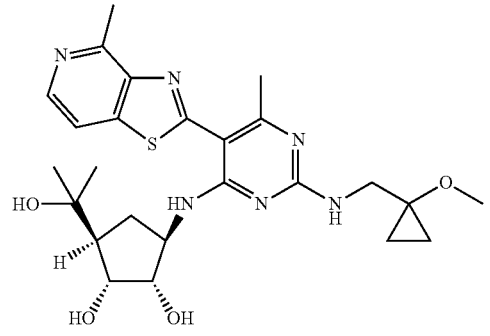
5260	
5256	
5261	
5257	

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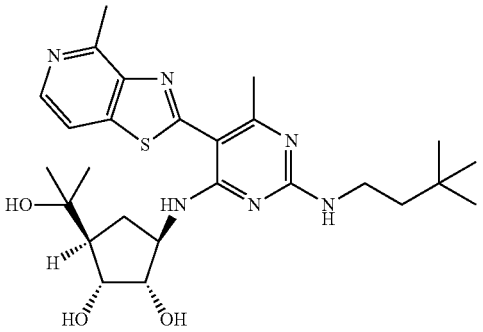
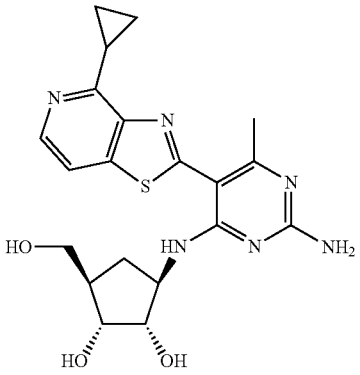
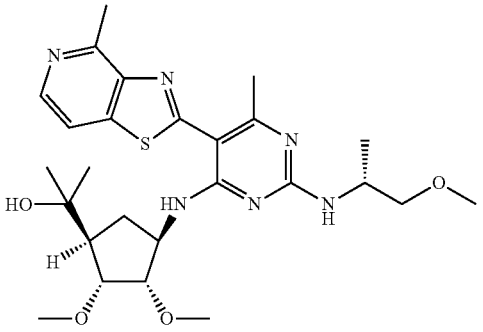
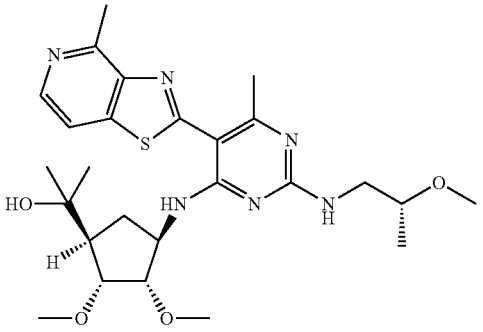
5262	
5258	
5263	
5264	

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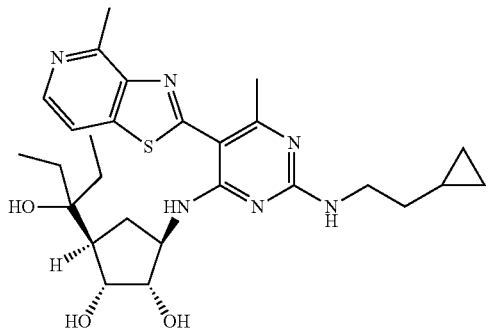
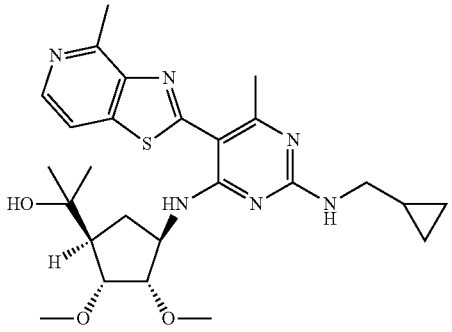
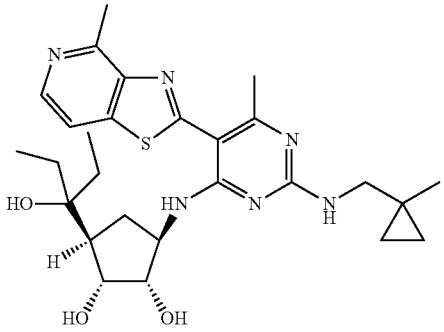
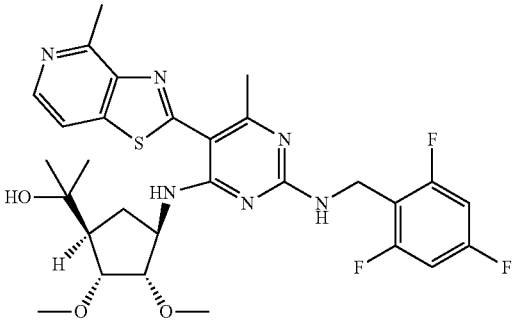
Compd #	Structure
5269	
5265	
5270	
5266	

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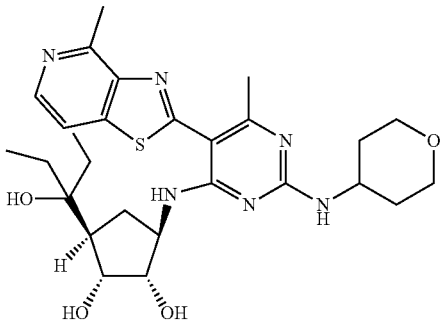
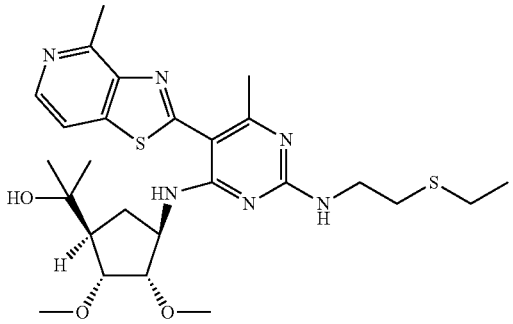
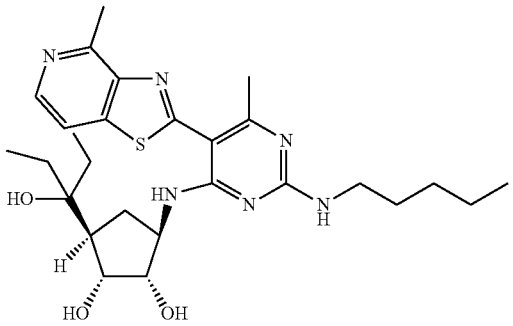
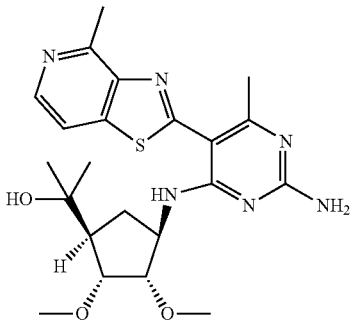
5271	
5267	
5272	
5268	

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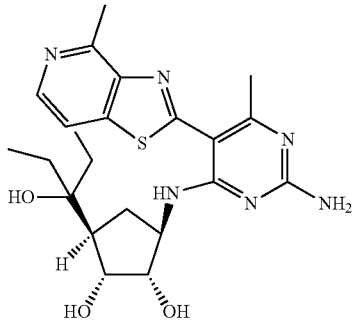
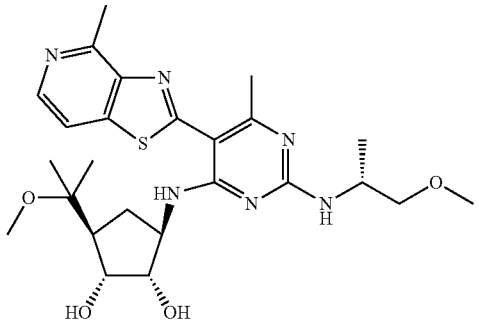
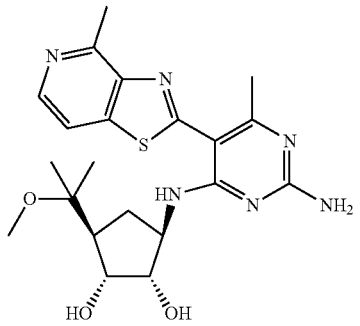
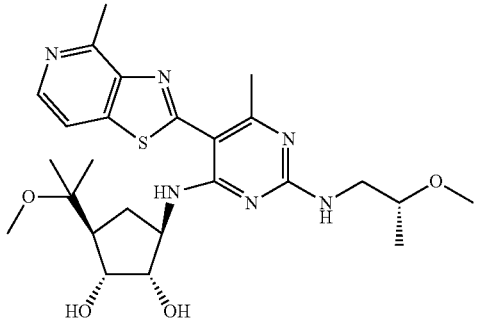
5273	
5274	
5279	
5275	

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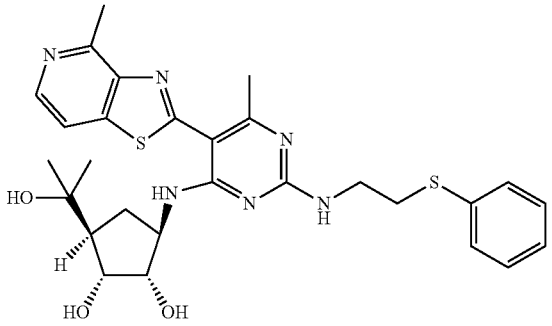
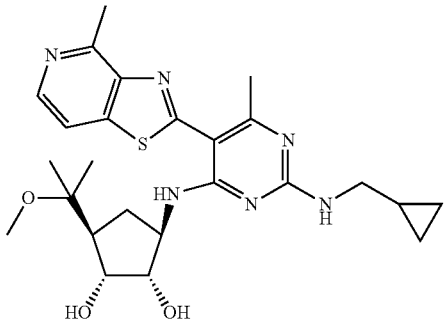
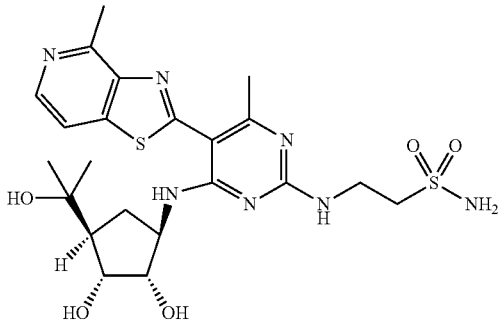
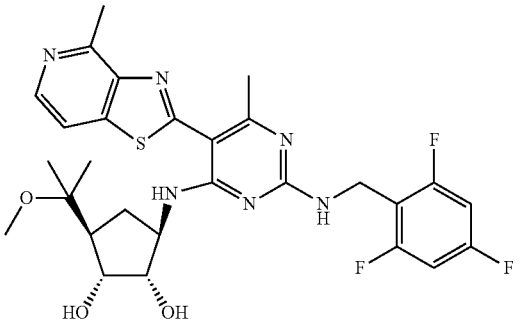
5280	
5276	
5281	
5277	

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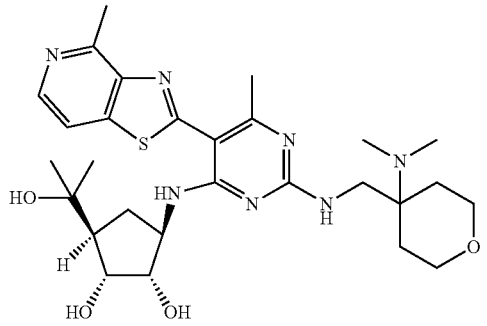
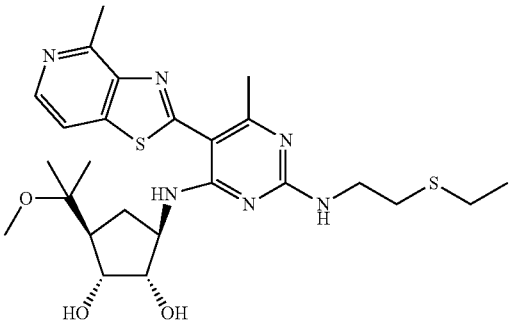
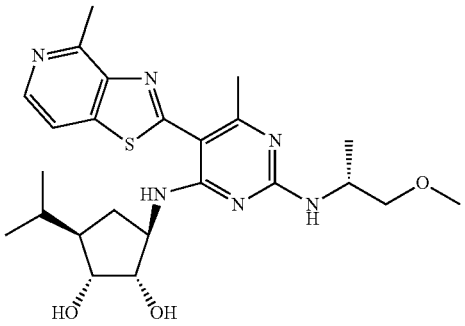
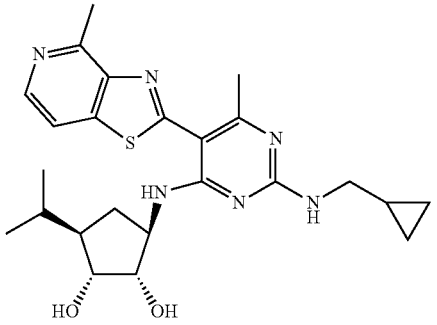
5282	
5278	
5283	
5284	

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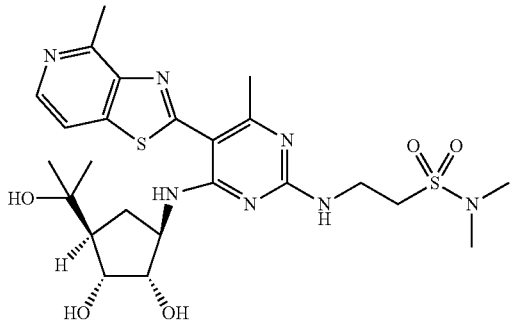
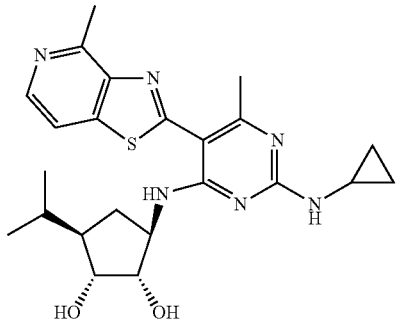
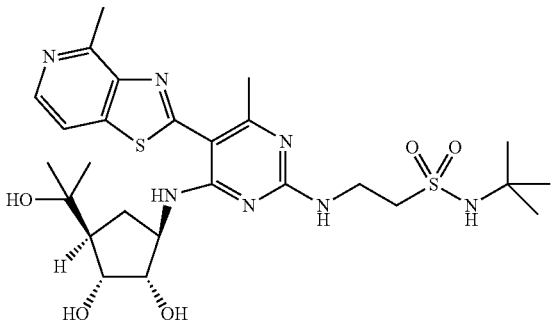
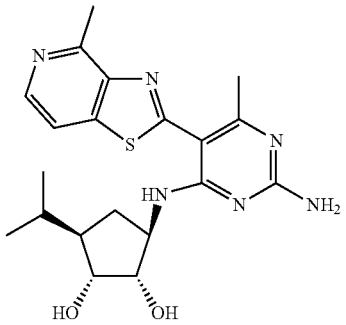
5288	
5285	
5289	
5286	

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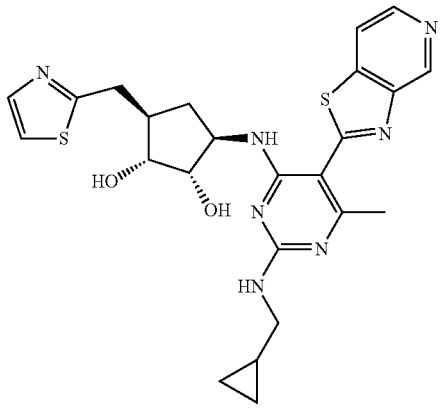
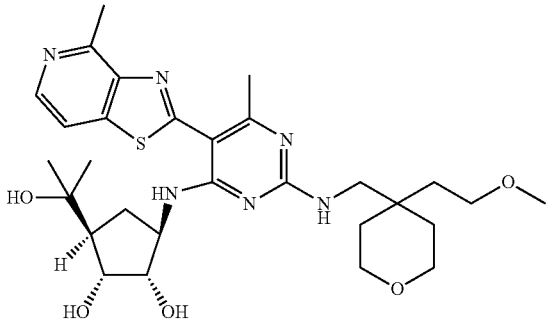
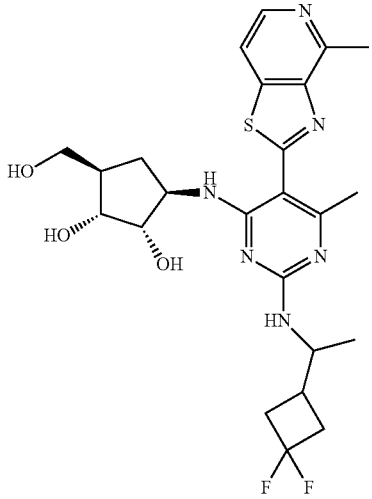
5290	
5287	
5291	

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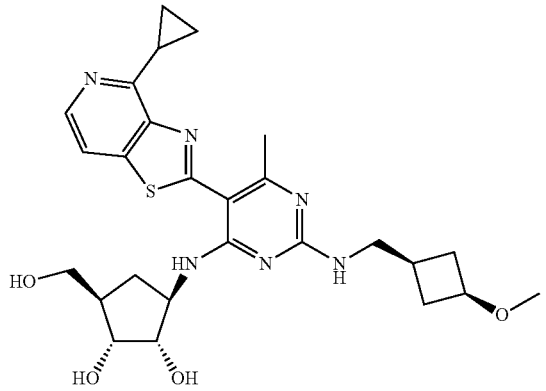
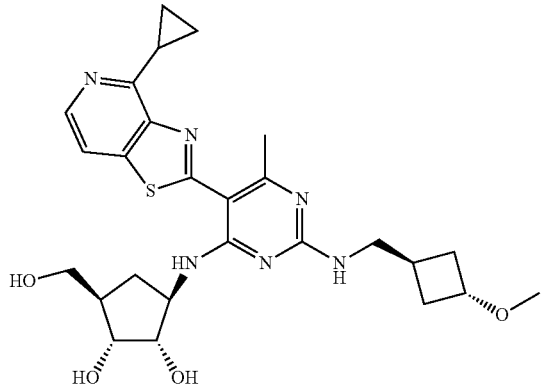
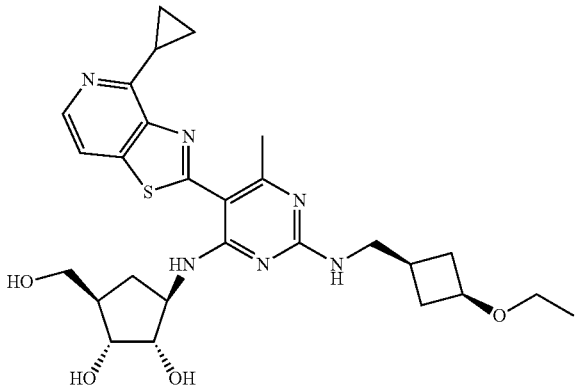
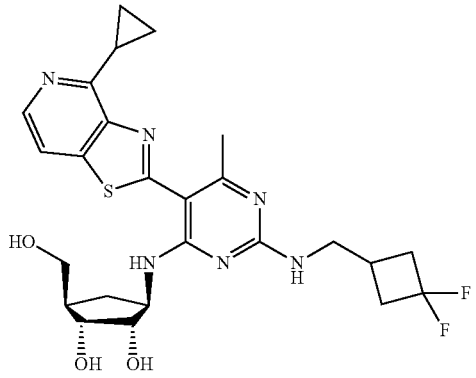
5292	
5296	
5293	
5297	

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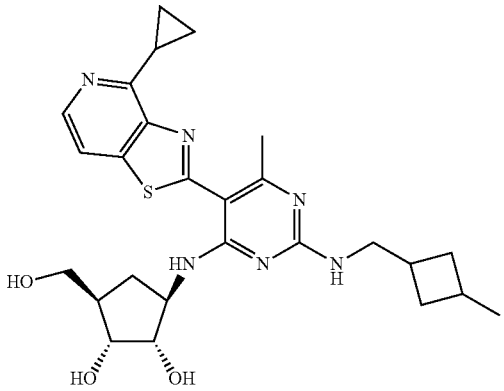
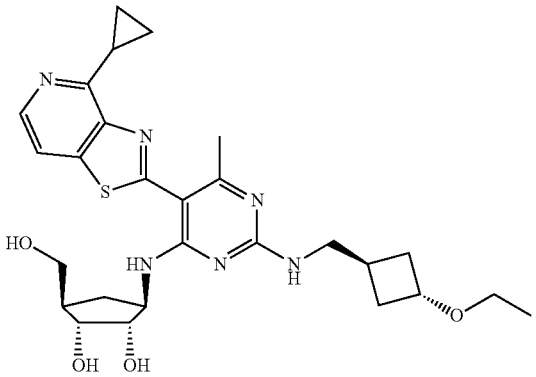
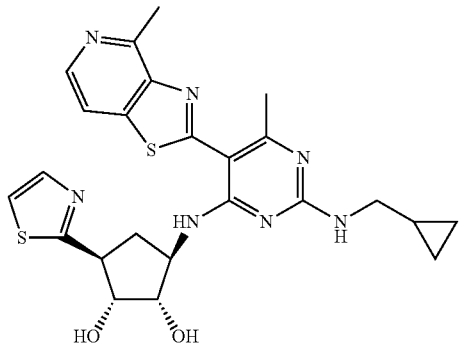
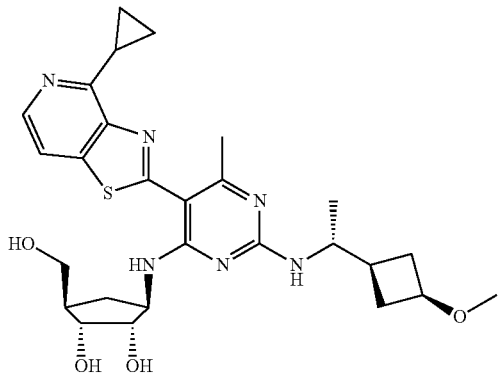
5294	
5298	
5295	
5299	

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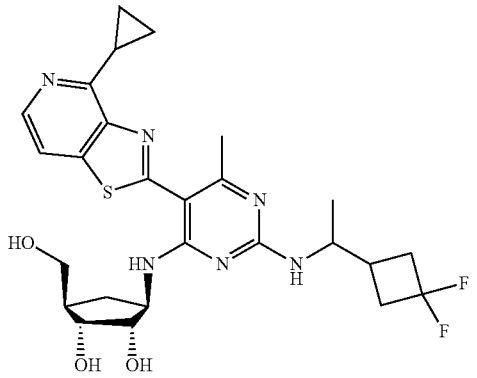
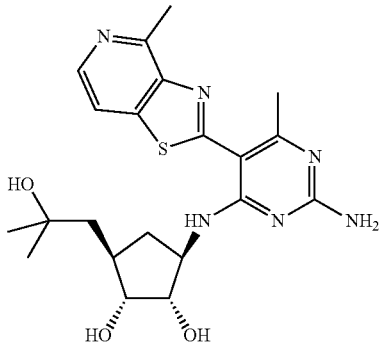
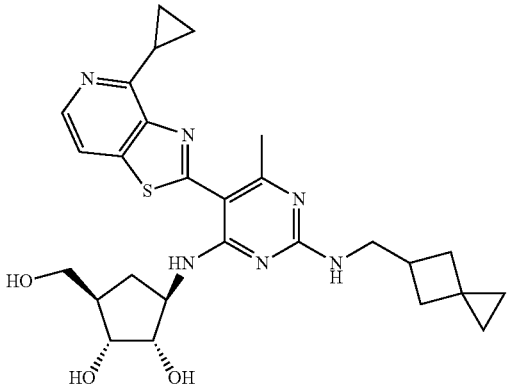
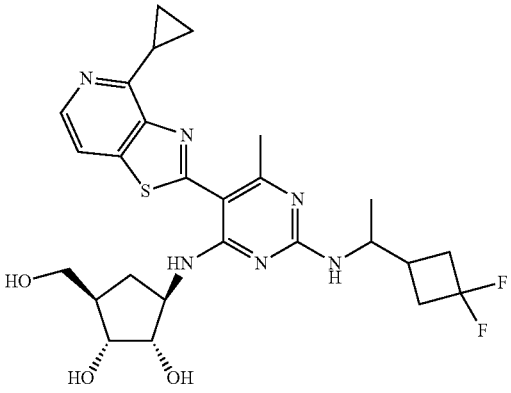
5300	
5304	
5301	
5305	

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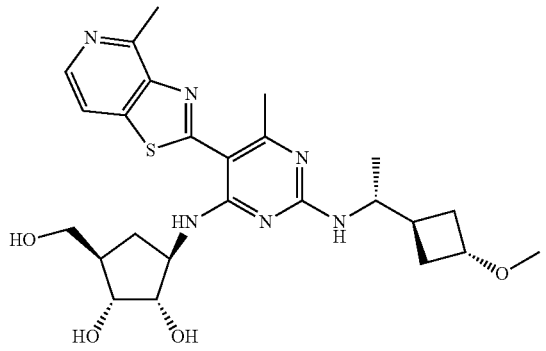
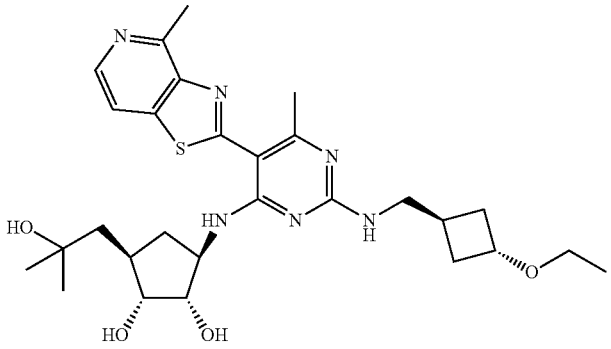
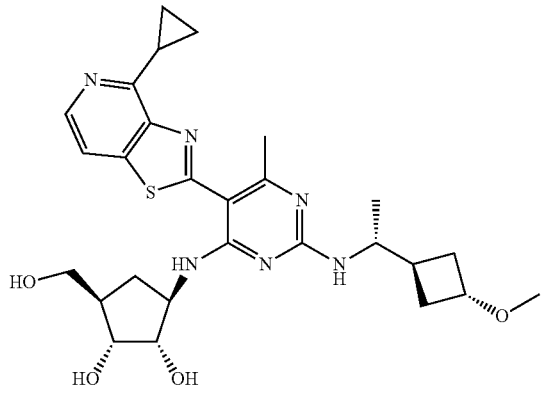
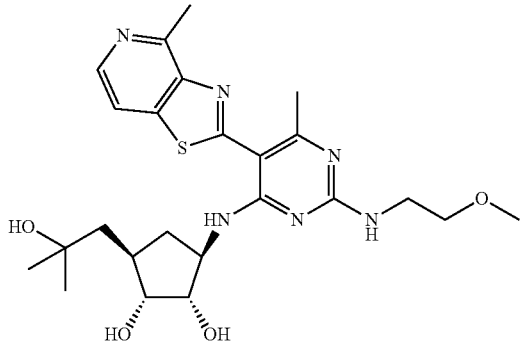
5302	
5306	
5303	
5307	

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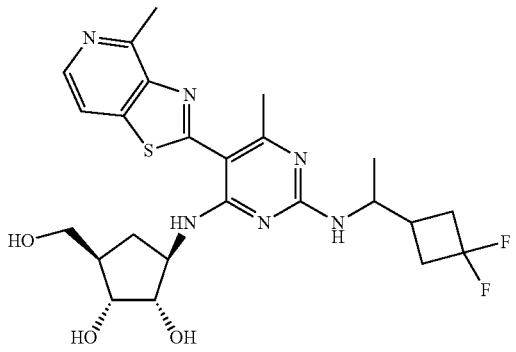
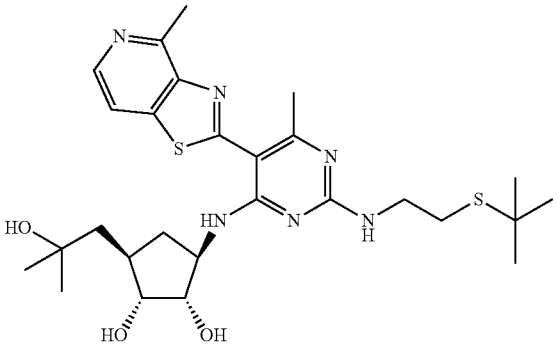
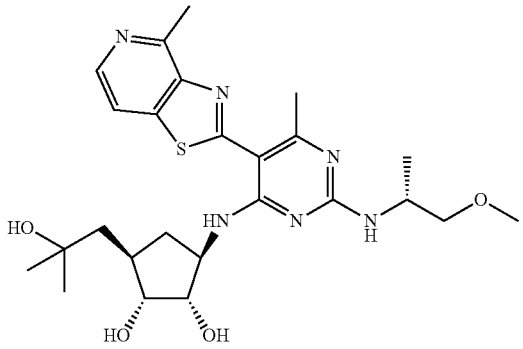
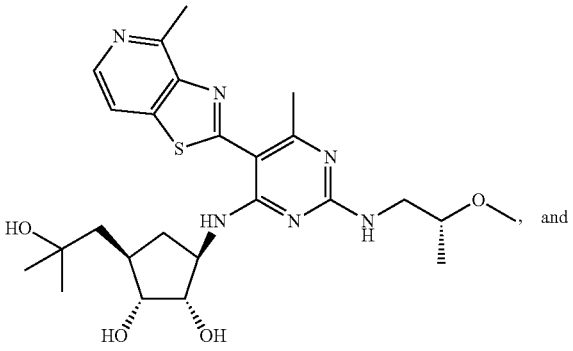
Compd #	Structure
5308	
5309	
5310	
5311	 , and

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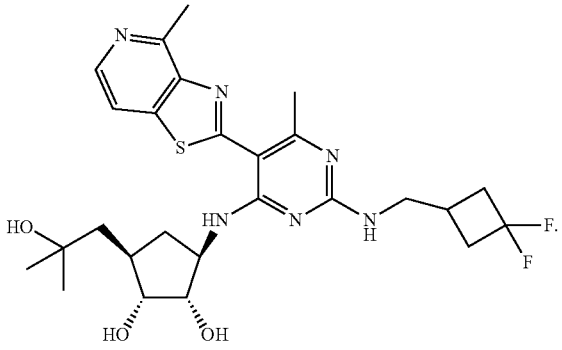
5312	

2. A pharmaceutical composition comprising at least one compound according claim **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

3. The pharmaceutical composition of claim **2**, further comprising at least one additional therapeutic agent selected from the group consisting of: an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral protease inhibitor, a virion production inhibitor, an immunosuppressive agent, an antiviral antibody, a CYP-450 inhibitor, an antiviral booster, and an antiviral sensitizer.

4. The pharmaceutical composition according to claim **2**, further comprising therapeutically effective amounts of pegylated interferon and ribavirin.

5. A method of treating an HCV infection comprising administering to a patient in need of such treatment a therapeutically effective amount of at least one compound according to claim **1**, or a pharmaceutically acceptable salt thereof.

6. The method according to claim **5**, further comprising administering a therapeutically effective amount of at least one additional therapeutic agent useful for treating a viral infection or a virus-related disorder, wherein said at least one additional therapeutic agent is selected from the group consisting of: an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral protease inhibitor, a virion production inhibitor, an immunosuppressive agent, an antiviral antibody, a CYP-450 inhibitor, an antiviral booster, and an antiviral sensitizer.

7. The method according to claim **5**, further comprising administering therapeutically effective amounts of pegylated interferon and ribavirin.

* * * * *